The development of a computation / mathematical model to predict drug absorption across the skin

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King's College London

Title: The development of a computation / mathematical model to predict drug absorption across the skin

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THE DEVELOPMENT OF A MATHEMATICAL / COMPUTATIONAL MODEL TO PREDICT DRUG ABSORPTION ACROSS THE SKIN

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Thesis submitted in accordance with the requirement
for the Degree of Doctor of Philosophy

September 2012

I hereby declare that the work presented in the thesis is my own.

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September 2012

Abstract

The ability to predict accurately the dermal permeation of a chemical is important for the development of new therapeutic formulations in transdermal drug delivery and also for the assessment of the potential risks of environmental chemicals and agents used in cosmetics industry. There have been a large number of studies investigating skin permeability, both experimentally- and theoretically-based. The experimental measurement of skin permeability is a time-consuming and difficult process and, when put in the context of the great numbers of chemicals that may come into contact with the skin, it is also costly. As a consequence, there has been a great interest over the past years to 'predict' the ability of a compound to cross the skin using its physicochemical characteristics and a number of mathematical models have been reported. Most models are based on experimental data, with skin permeability linearly correlated to the physicochemical properties and / or molecular structure parameters of the chemical compounds. A multilinear regression method is often used to fit available experimental data and such empirical models are referred to as quantitative structure-property relationships (QSPRs). Many QSPR models relate skin permeability to the physicochemical properties of the solutes while others use molecular structure properties. Successful application of such models can realise a marked reduction in the number of potentially therapeutic molecules requiring synthesis and validation since they can be precluded from study on the basis of their predicted lack of skin permeability. In terms of skin permeability data with respect to QSPR analysis, the science has not been developed significantly since the publication of what is now universally known as the Flynn dataset (Flynn 1990). The most widely cited model that was developed on the basis of the Flynn dataset was the Potts and Guy (1992) model and since then a number of alternative models have been developed using the Flynn and other subsequently assembled datasets.

The aim of this study was to determine the limitations of the existing models and to address any deficiencies by the development of new mathematical models. Databases containing measured and well-defined skin absorption data are a key first step in the development of QSPR models, which might improve the understanding of the dermal absorption process for chemicals. Therefore the first objective was to develop a more stringently controlled database that included parameters derived under more strictly defined experimental conditions. These data would then enable the current models to be re-evaluated and accordingly a detailed analysis of all the available *in vitro* dermal absorption data to be conducted with a view to classifying the data according to the corresponding experimental conditions employed so as to produce a number of data subsets.

Subsequently, advanced computational regression modelling methods, such as the Gaussian method, were applied to develop the most efficient model in terms of statistical fit. The Gaussian process (GP) has not been applied previously to skin permeability data. The potential of including additional descriptors such as molecular weight, lipophilicity, Fedors' solubility parameter, hydrogen bond acceptor and donor capacity into any developed equations with a view to improving accuracy was investigated. For comparison reasons, a new linear regression model was also developed based on the above-mentioned 5 additional descriptors (5f linear regression model). The GP model yielded a predictive model that provided a significantly more accurate estimate of skin absorption than previous models across a wider range of molecular properties. It proved to be particularly capable of providing excellent predictions where

previous studies have shown QSPRs to fail: at high log P and MW of penetrants. The results indicate that, in terms of statistical performance, the Gaussian model was better than the 5f model. This suggested that, statistically, a nonlinear approach, as employed herein, is more appropriate for analysis than linear techniques. The relative accuracy of the GP, 5f linear regression and Potts and Guy (1992) models were also compared. Permeation data were obtained under carefully controlled conditions and these were correlated to values calculated from the application of various models. Apart from comparing the experimental values with those predicted from each model, all deviations were recorded and the performance of each model was assessed. The flux values of two drug candidates, ibuprofen and furosemide, determined using the GP and 5f models, agreed well with those obtained experimentally. However, procaine hydrochloride diffused at a rate that was slower than that predicted by all models and paracetamol diffused at a much higher rate than was predicted from the GP model. The latter results could possibly be due to the relatively small degree of paracetamol ionisation. As a result, the effect of ionisation on permeability was measured by determining the flux of a single ionisable drug at three different pH values. The experimental results obtained were compared with the linear ionisation model, in which log D values were incorporated into the equation instead of log P values. It was concluded that ionisation, together with nonlinearity, were two of the most important factors that require further consideration when designing new models to predict dermal absorption.

A series of more strictly defined databases was successfully assembled during the course of this study and used to propose novel computational models for dermal absorption. Such models showed satisfactory predictive capacity but do require further development, particularly in the case of ionisable compounds. However, the development of such databases alone is of great use for future model development.

Publications

Refereed Papers

- Yi Sun, Gary P. Moss, Maria Prapopoulou, Rod Adams, Marc B. Brown and Neil Davey (2008) Prediction of Skin Penetration Using Machine Learning Methods, in *Data Mining, IEEE International Conference on Data Mining*: 1049-1054.
- Gary P. Moss, Yi Sun, Maria Prapopoulou, Neil Davey, Rod Adams, W. John Pugh and Marc B. Brown (2009) The application of Gaussian processes in the prediction of percutaneous absorption. *J.Pharm.Pharmacol.* 61: 1147-1153.
- Lun Tak Lam, Yi Sun, Neil Davey, Rod Adams, Maria Prapopoulou, Marc B. Brown and Gary P. Moss (2010) The Application of Feature Selection to the Development of Gaussian Process Models for Percutaneous Absorption. *J.Pharm.Pharmacol*. 62: 738-49.
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- Gary P. Moss, Yi Sun, Simon C. Wilkinson, Neil Davey, Rod Adams, Gary P. Martin, M. Prapopopolou and Marc B. Brown (2011) The application and limitations of mathematical modelling in the prediction of permeability across mammalian skin and polydimethylsiloxane membranes. *J.Pharm.Pharmacol.* 63: 1411-27.

Conference Communications

- Yi Sun, Gary P. Moss, Maria Prapopoulou, Rod Adams, Marc B. Brown and Neil Davey (2010) The Application of Gaussian Processes in the Prediction of Percutaneous Absorption for Mammalian and synthetic Membranes, in *Proceedings of ESANN (European Symposium on Artificial Neural Networks)*.
- Yi Sun, Lun Tak Lam, Gary Moss, Maria Prapopoulou, Rod Adams, Neil Davey, David Gray and Marc Brown (2010) Predicting drug absorption rates through human skin, in *Proceedings of WCCI*, Barcelona.

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Glossary of Abbreviations

^{14}C	radiolabelled carbon	C_{union}	union concentration
A	area of application	C_v	drug concentration in the formulation
A	frequency	CV	canonical variable
AAPS	Americal Association of Pharmaceutical Sciences	C_w	concentration of the chemical in water ($mgcm^{-3}$)
ADME	absorption distribution metabolism and elimination	D	diffusion coefficient, or diffusivity
ANN(s)	artificial neural network(s)	DBDPO	decabromodiphenyl oxide
ANOVA	a one-way analysis of variance	DDT	dichlorodiphenyltrichloroethane
BADGE	bisphenol A diglycidyl ether	DEHP	(2-ethylhexyl) phthalate
BP	butyl paraben	Ea	activation energy
BSA	bovine serum albumin	ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
C	concentration of the diffusing substance	EDETOX	Evaluations and Predictions of Dermal Absorption of Toxic Chemicals
C12GE	dodecyl glycidyl ether	$E[f(x)]$	mean
C_{app}	applied concentration	EPA	Enviromental Protection Agency
CC	canonical correlation	ESANN	European Symposium on Artificial Neural Networks
CCA	canonical correlation analysis	F	Fisher's statistic
C_d	drug concentration on the other side of the membrane	FDA	Food and Drug Administration
CEFIC	*Conseil Européen des Fédérations de l'Industrie Chimique* - European Chemical Industry Council	FIP	International Pharmaceutical Federation
CF	caffeine	Fl	flux
ChemID	chemical identification	GC	gas chromatography
C_{ion}	ion concentration	GLP	good laboratory practice
CL	clearance	GP	Gaussian process
C_{max}	maximum concentration	GPRf5	Gaussian process regression with 5 features
CORR	correlation coefficient	h	thickness
C_p	steady-state plasma levels	Ha	hydrogen bond acceptor
C_{sat}	the saturated concentration of a compound in the vehicle	Hb	hydrogen bond

HCL	hydrochloric acid
Hd	hydrogen bond donor
HDDGE	1,6-hexanediol glycidyl ether
HEP-NTX	NTX-3 heptanoate
HIV	human immunodeficiency virus
HPLC	high-performance liquid chromatography
I	dermally absorbed intake (mg)
IGC	inhibition growth concentration
IMP	isopropyl myristate
ION	improvement over a naïve model
ISDN	isosorbide dinitrate
J	rate of transfer per unit area of the surface - the flux
Js	steady state flux
$k(x_i; x_j)$	covariance function
K_a	ionisation constant
K_{aq}	permeation coefficient of watery epidermal layer
K_m	vehicle / stratum corneum partition coefficient
KNN	K-nearest-neighbour regression
K_p	permeability coefficient
K_p^{fv}	permeability associated with free-volume type of diffusion through lipid bilayers
K_{pion}	permeability coefficient ion
$K_p^{lateral}$	permeability of hydrophobic solutes due to lateral diffusion of lipids
K_{pcl}	permeation coefficient of the protein fraction of stratum corneum
K_p^{pore}	solute permeability through pores
K_p^{shunt}	solute permeability through shunts
K_{psc}	permeation coefficient of lipid fraction of stratum corneum
K_{punion}	permeability coefficient union
l	characteristic length-scale
LFER(s)	linear free-energy relationship(s)
LOD	limit of detection
log D	distribution coefficient
$\log P^{ion}$	partition coefficient of ionised molecules
$\log P^{I}$	partition coefficient for ionised molecules
LOQ	limit of quantification
LSE(s)	living skin equivalent model(s)
MAPE	mean absolute percentage error
ME	mixture-of-experts
MLR	multiple linear regression
MP	methyl paraben
MPt	melting point
MSE	mean squared error
MV	molecular volume
MW	molecular weight
N, n	number of observations
nArCOOR	number of esters / aromatic
nHDon	number of H.donor
NLL	negative log loss
NMSE	normalized mean squared error
NN	neural networks
nQC	number of quarternary C
nRCOOR	number of esters / aliphatic
NSAID	non-steroidal anti-inflammatory drug

N_{test}	test data	SLN	single layer network
NTX	naltrexone	SMILES	simplified molecular input line entry specification
oCGE	o-cresyl glycidyl ether	SP	Fedors' solubility
OECD	Organization for Economic Co-ordination and Development	SPSS	Statistical Package for the Social Sciences
P	partition coefficient	SRC	Syracuse Research Corporation
PA	percutaneous absorption	SS	semi-solid
PBS	phosphate buffer solution	SUPAC	Scale-Up and Post-Approval Changes
PC	principal component	T	temperature
PCA	principal component analysis	TDCCP	tri(2,3-dichloropropyl) phosphate
PEG	polyethylene glycol	TDS	transdermal delivery system
pKa	dissociation constant	TEWL	transepidermal water loss
P^N	partition coefficient for neutral molecules	THC	Δ-tetrahydrocannabinol
P_{ow}	octanol/water partition coefficient	T_{lag}	lag time
PubMed	Public Medline	USEPA	U.S. Environmental Protection Agency
Q	cumulative amount of penetrant	UV	ultraviolet
QSAR(s)	quantitative structure-activity relationship(s)	V_w	calculated Van der Waals volume
QSPR(s)	quantitative structure-permeabiltiy relationship(s)	WHIM	weighted holistic invariant molecular
R	molar gas constant	X	spatial co-ordinate
R^2	regression coefficient	α	hydrogen bond donor acidity
R^2CV	cross-validated (leave-one-out) multiple correlation coefficient	α	thermodynamic activity
RC	retardation coefficient	β	hydrogen bond acceptor basicity
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals	γ	effective activity coefficient
RPI	relative polarity index	δij	Kronecker delta
RT	room temperature	Δu	substituent fragment constant
S	standard error	ΔV	fragmental molar volume constant
SC	stratum corneum	Π^*	dipolarity
SD	standard deviation	σf	signal variance
SE	standard error	σn	*noise variance*

Acknowledgements

I am deeply grateful to my supervisors for their assistance on this project. Professor Gary P. Martin's pursuit for perfection and work ethic always kept this project moving forward. Gratitude is also due to Professor Marc Brown for his patience, understanding and keen motivational skills as well as for his assistance in reviewing this manuscript. Thanks are due to Dr Gary P. Moss for his willingness to partake in scientific debate and to Dr Yi Sun for her fruitful support with regards to mathematical modeling. I whole-heartedly thank all my fellow students of the pharmaceutics group for all their emotional and practical support.

I would like to thank my husband Haris Zachariou for his personal support and great patience throughout these years. This thesis is dedicated to my father Andreas Prapopoulos who inspired me to further expand my intellectual horizons and supported me in every step of the way.

Chapter One

General Introduction

1.1. BACKGROUND AND RATIONALE

Transdermal (percutaneous, skin) absorption is a global term that describes the transport of chemicals from the outer surface of the skin to the systemic circulation (OECD 2004a). It is a complex process by which a substance is transported across the skin and taken up into the living tissue of the body. The skin is a multilayered biomembrane with particular absorption characteristics. It is a dynamic, living tissue and as such its absorption characteristics are susceptible to constant change.

Some circumstances in which dermal absorption considerations are important include the development of transdermal drug delivery systems (e.g. for analgesia), dermatological formulations for localised transport (e.g. psoriasis), safety assessment of cosmetics and risk assessment of occupational, environmental, or consumer exposure. Despite all these applications involving dermal absorption, they have different aims and approaches. For some drugs, it may be important that the substance passes through the skin and into the bloodstream. However, in the case of cosmetics and sunscreen lotions, it may not be necessary or desirable for the product to penetrate the skin; instead, the product may be effective by simply remaining in / on the upper skin layer. In occupational and consumer scenarios, the skin absorption of chemicals and pesticides needs to be minimised. Risk assessments are usually performed to determine the extent to which exposure to a particular substance is acceptable and therefore the extent to which the substance is safe to use. For many chemicals, there is no information on the risks of dermal absorption.

The development of new forms of drug delivery is one of the most active areas in applied pharmaceutical research. The use of the transdermal pathway for systemic treatments has been shown to be a viable alternative to the classic parenteral and enteral routes. Transdermal delivery offers several advantages, including the avoidance of hepatic first-pass effect and the maintenance of steady-state plasma levels to provide long term therapy from a single dose. The transdermal pathway is of potential interest for those patients who cannot take medicines by themselves, or when oral administration of drugs may be inadvisable, such as in functional alterations of gastric motility or in nausea and vomiting.

Nevertheless, transdermal therapy also has its disadvantages. The excellent barrier properties of the skin may prevent the entry of drug molecules from the external environment. Compounds may activate allergic responses and the drug may be metabolised by microflora on the skin's surface or by enzymes in the skin. Another disadvantage is the variability in skin permeability and, as a consequence, transdermal therapeutic systems have been developed to control the delivery of the drug and minimise intersubject variation. Relatively few drugs are able, at least by passive diffusion alone, to penetrate the skin at a rate and amount sufficient to elicit a therapeutic effect. Consequently, in order to determine which drugs are likely to be appropriate candidates to develop for delivery via this route, the skin permeation characteristics of such compounds require determination and evaluation.

Chemicals present in workplaces or the environment may come into contact with the skin and be absorbed. Although interest in dermal absorption for risk assessment purposes is comparatively recent, research into the factors involved in the passage of compounds through the skin has been conducted for other purposes. The

steps between the presence of a chemical in the environment and systemic exposure may be divided into two phases (Johanson 2003). The first phase is the dermal exposure to the chemical (amount, area, duration). This is affected by a number of factors, such as the properties of the chemical, the work process, the individual's behaviour and work practices, type of clothing, type of protective equipment, etc. The second phase involves possible consequent systemic exposure, i.e. dermal absorption.

Therefore, it is useful to be able to predict the way in which materials penetrate the skin for both toxicological and therapeutic reasons. Percutaneous absorption can be studied with *in vitro* methods, since it is possible to maintain the barrier properties of the stratum corneum in excised skin. Such studies are becoming increasingly acceptable to regulatory agencies with respect to the provision of percutaneous absorption data for drugs, cosmetics, pesticides and industrial chemicals (Howes et al. 1996). However, there has been much interest in the possibilities available to predict dermal absorption and to avoid unnecessary and costly *in vitro* and *in vivo* testing. This is partly due to ethical difficulties with respect to human and animal experiments and partly due to economic and time considerations. Experiments are lengthy, since they are carried out using individual compounds, usually over extended time spans. There are also difficulties in obtaining excised human skin, which is the best membrane to use for *in vitro* measurements. As a consequence, there has been considerable interest, particularly during the past two decades, in developing methods to model dermal penetration. One of the principal strategies developed to avoid unnecessary and costly *in vitro* testing is the use of Quantitative Structure-Property Relationships (QSPRs) that are used mainly to predict steady-state permeabilities. QSPRs are widely used in science to correlate statistically selected, relevant physicochemical properties of compounds with their biological activities. Quite a number have now been developed specifically to model skin permeation and this field has been the subject of comprehensive reviews (Moss et al. 2002; Vecchia & Bunge 2003b). Nonetheless, these models possess limitations and hence need further refinement since they have not reached the stage of being accepted as having high predictability. This is due in part to the fact that the data upon which QSPRs are based for the prediction of percutaneous penetration are not ideal. The permeability coefficients available in the literature are not always measured under carefully controlled experimental conditions leading to inter- and intralaboratory variations.

Furthermore, the choice of certain data as outliers and their exclusion from such datasets can very greatly influence the apparent quality of the QSPRs developed on the remaining data points. Even when it is possible to reasonably argue that certain substances or classes of substances can be expected to be anomalous, it is never completely satisfactory to remove data primarily because their behaviour does not comply with a standard model (Fitzpatrick et al. 2004). Taking into consideration all the above, as well as some other factors such as the use of additional inputs in the models, it can easily be concluded that new and more descriptive *in silico* models should be further developed for future predictions. It is apparent that transdermal drug delivery is a very complex issue, as many strongly interrelated variables are involved. Nevertheless, this can be rationalised to a certain extent by applying a systematic approach to key factors as skin structure and function and to the selection of the most important parameters that can influence percutaneous absorption. Thus, an important starting point is to appreciate the structure of the skin.

1.2. SKIN STRUCTURE AND FUNCTION

1.2.1. Anatomy and Physiology of Human Skin

The skin is considered an organ, since it consists of several kinds of tissues that are structurally arranged to function together. It is more than a convenient layer separating the contents of the body from the outside world. The skin is the largest organ of the body, covering over 7600 cm^2 in the average adult, and accounts for approximately 7% of a person's body weight. The skin is of variable thickness, averaging between 1.0 and 2.0 mm. It is thickest on the parts of the body exposed to wear and abrasion, such as the soles of the feet and palms of the hands, where it is about 6 mm. It is the thinnest on the eyelids, external genitalia and tympanum, where it is approximately 0.5 mm. Skin is composed of three principal layers, the epidermis, the dermis and subcutaneous fat. (Figure 1.1) The subcutaneous fat is located below the dermis and acts as a fat storage layer, having insulating and protecting (shock absorbing) properties. It does not play a role in percutaneous absorption because it is located below the vascular system, which is found in the dermis. The dermis is an acellular connective tissue that supports blood vessels and nerves. Hair follicles, sebaceous glands and sweat glands stem from here to reach the skin surface. The transport of solutes in this area is rapid, moving via microvascular blood vessels into the systemic circulation. Above the dermis is located the epidermis.

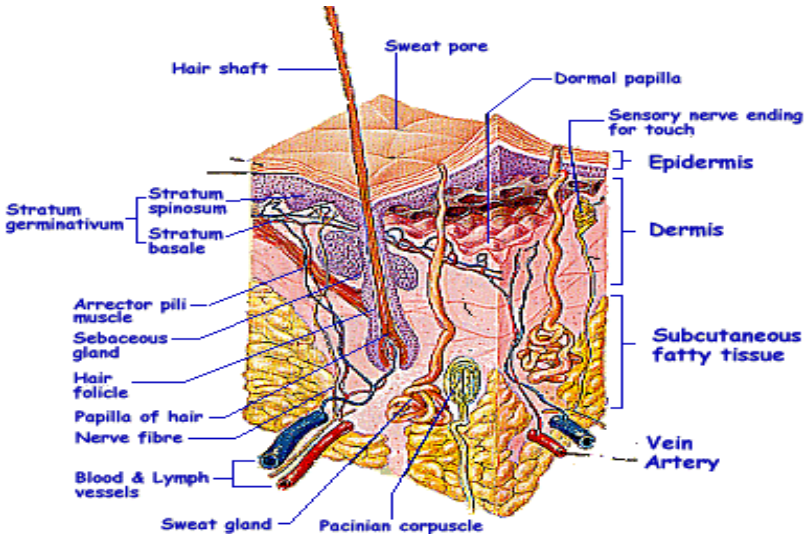


Figure 1.1. Structure of the skin (www.avro.co.za).

1.2.1.1. Epidermis

The epidermis is the outermost layer of the skin and its thickness varies according to skin type and anatomical site (Bloom & Fawcett 1994). It is the superficial protective layer of the skin and is composed of stratified squamus epithelium. It is comprised of either four or five layers, depending on its anatomical location (Van de Graaff 1995). The epidermis of the palms, soles and lips has five layers because these areas are exposed to more friction. The epidermis of all other areas of the body has only four layers, stratum basale, stratum

spinosum, stratum granulosum and stratum corneum (Figure 1.2). The additional fifth layer, the stratum lucidum, when present, is located directly under the stratum corneum.

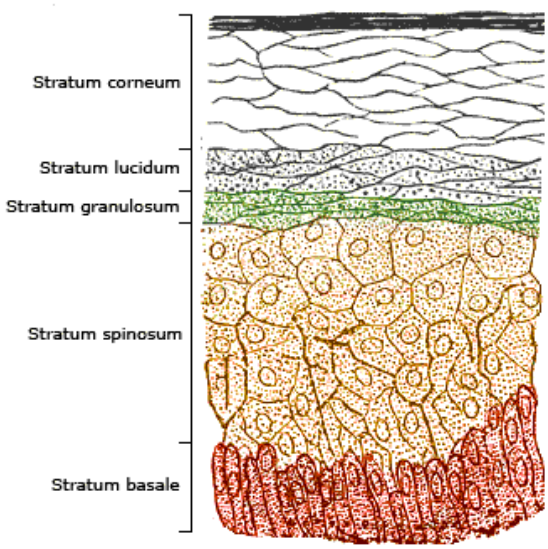


Figure 1.2. Structure of the epidermis (www.hse.gov.uk/skin/images/outersection.gif).

The stratum basale (basal layer) comprises the innermost layer of the epidermis, adjacent to the dermis. It is composed of a single layer of cells in contact with the dermis. The stratum basale consists of keratinocytes, melanocytes, tactile cells and the non-pigmented granular dendrocytes. Keratinocytes are specialised cells that produce keratin, which toughens and waterproofs the skin. Melanocytes are specialised epithelial cells that synthesise the pigment melanin, providing a protective barrier to the ultraviolet radiation in the sun light. Tactile cells are oval nucleated cells that are in close contact with the expanded ends of nerve fibres in the deeper layers of the epidermis and dermis of some parts of the body and probably serve a tactile function. Tactile cells are sparse in comparison with keratinocytes and melanocytes, whereas non-pigmented granular dendrocytes are scattered throughout the stratum basale.

The stratum spinosum (prickly layer) contains several stratified layers of cells. The cells of this layer have a polyhedral shape, are held together by inter-cellular bridges (or prickles) and become flattened towards the top. The spiny appearance of this layer is due to the changing shape of the keratinocytes. There is limited mitosis in the stratum spinosum and this layer together with the stratum basale are collectively referred to as the stratum germinativum (Van de Graaff 1995). Prominent nuclei and cytoplasmic basophilia indicate active protein synthesis. A fibrillar protein aggregates in these cells to form intracellular fibrils known as tonofibrils, which converge upon the desmosomes of the prickle cells. These tonofibrils become more prominent toward the stratum granulosum.

The stratum granulosum (or granular layer) is a layer of the epidermis found between the stratum corneum (and possibly stratum lucidum) and stratum spinosum (James et al. 2005). In this layer, keratinocytes are called granular cells and contain keratohyalin and lamellar granules (McGrath & McLean 2005). The cells in the stratum granulosum have lost their nuclei and are characterised by dark

clumps of cytoplasmic material. There is a lot of activity in this layer as keratin proteins and waterproofing lipids are being produced and organised.

The stratum lucidum, where present between the stratum granulosum and the stratum corneum, can provide an additional layer. The nuclei, organelles and cell membranes are no longer visible in the cells of the stratum lucidum and, therefore, histologically this layer appears to be clear. The stratum lucidum is so thin that there is debate currently that the layer is an artefact of the electron microscope and may not in fact exist. It is 'found' only in the lips and in the thickened skin of the soles and palms.

The stratum corneum comprises the outermost layer of the epidermis and it provides the primary barrier to permeation of most drugs and chemicals (Scheuplein & Ross 1976; Michaels et al. 1975). The stratum corneum is between 10 and 50 μm thick and contains dead keratinised cells (corneocytes) with lipid lamellae filling the intercellular regions. It is composed of 25 to 30 layers of flattened, scale-like keratinised cells, which are continuously shed as flake like cell residues. This surface layer is cornified and is the real protective layer of the skin. The architecture of the horny layer may be modelled as a wall-like structure. In this model, the keratinised cells function as protein 'bricks' embedded in lipid 'mortar.' (Figure 1.3)

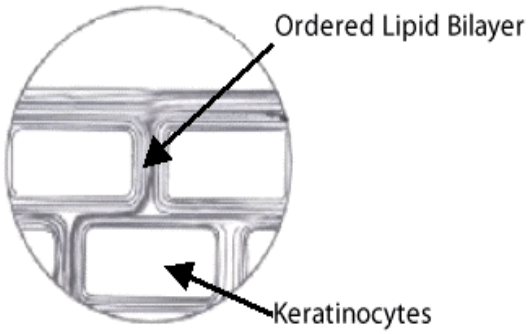


Figure 1.3. Structure of the stratum corneum (www.sontra.com/technology, February 2003).

The 'mortar' (extracellular lipid) consists of a structured complex containing several groups of lipids. These include water, ceramides, free fatty acids, triglycerides, phospholipids, glycosphingolipids and cholesterol sulphate. The relative amount of each lipid type present in extracellular lipid varies according to the body region. Stratum corneum lipids are arranged in multiple bilayers. It has been suggested that the amphiphilic material present in the lipid fraction, such as polar-free fatty acids and cholesterol, maintains the bilayer form. The precise molecular arrangement of the intercellular lipid is still not completely known. The 'bricks' are the dead, flattened cells of the horny layer, the keratinocytes, which contain very little lipid. The keratinocytes, connected together in a planar array by desmosomes, are thin platelets filled with polar protein strands woven into compact and dense keratin fibres. Keratin is not a single substance but a complex mixture of proteins whose most important chemical feature is the preponderance of the sulphur containing diamino acid cystine (Walters 2002). The compactness of the keratinocytes and the limited amount of intercellular lipid results in the low permeability of the stratum corneum.

1.2.1.2. Dermis

The dermis is a tough supportive connective tissue matrix containing numerous specialised structures. The dermal thickness varies being thinnest (0.6 mm) on the eyelids and thickest (3 mm or more) on the back, palms and soles (Van de Graaff 1995). The papillary dermis, the thin upper layer of the dermis, composed of loosely interwoven collagen, lies directly below and interdigitates with the epidermal rete ridges. Found deeper is the thicker reticular dermis with its coarser and horizontally-running bundles of collagen. Cells of the dermis, which are mainly fibroblasts, are separated by a complex mesh of extracellular material. There are also immune and inflammatory cells, nervous tissue and blood vessels present.

The extracellular matrix, synthesised by the fibroblasts, forms the major constituent of the dermis and is comprised primarily of collagen and elastin. Collagen fibres make up 70% of the dermis and give it structural toughness and strength. Collagen is an insoluble protein found throughout the body in the connective tissues that hold muscles and organs in place and in the skin; it supports the epidermis, lending it its durability. Elastin, a similar protein, keeps the skin flexible. This is the substance that allows the skin to spring back into place when stretched. Elastin fibres are loosely arranged in all directions. They are most prevalent near hair follicles and sweat glands and less so in the papillary dermis. Water is also found in the dermis. In fact, much of the body's water supply is stored there. When the amount of stored water is increased, the skin becomes tight and stretched as it expands to accommodate the surplus. The dermis contains dermal dendrocytes, which are dendritic cells with immune function; mast cells; macrophages; and lymphocytes. In addition, it provides support for the sweat, apocrine and eccrine glands. The sebaceous or oil glands are cylindrical structures that house the roots of the hair. The cutaneous blood supply has an essential function in the regulation of the body temperature and provides nutrients and oxygen to the skin, while removing toxins and waste products. Capillaries reach to within 0.2 mm of the skin surface and provide sink conditions for most molecules penetrating the skin barrier. Thus, the blood supply keeps the dermal concentration of a permeated drug very low and the resulting concentration difference across the epidermis provides the essential driving force for transdermal penetration.

1.2.1.3. Subcutaneous Fat

The subcutaneous fatty tissue merges with the overlying dermis. It is the innermost layer of the skin. Its thickness varies in different regions of the body and it is composed of loose connective tissue. This layer helps to regulate temperature, provides nutritional support and mechanical protection. It represents an energy source for the body. It also carries the principal blood vessels and nerves to the skin and may contain sensory pressure organs.

1.2.2. Skin Appendages

The skin contains a variety of appendages, mainly sweat glands, hair follicles and sebaceous glands. The fractional area available for drug absorption via the appendages is small, i.e. approximately 0.1%, and, thus, their contribution to steady state flux is considered to be insignificant (Barry 2001b).

1.2.2.1. Sweat Glands

These are simple coiled tubular glands divided into two principle types, eccrine and apocrine. Eccrine sweat glands are found all over the body covering about 200 cm^2 and totalling 2 to 5 million whereas apocrine glands are highly regionalised. Eccrine sweat glands produce sweat (pH 4.0-6.8) and may also secrete a watery mixture of salts, antibodies and metabolic wastes. The principle function of sweat is to prevent overheating of the body and, thus, help regulate body temperature. From a skin permeability viewpoint, acidic drugs would be ionised at pH 4.0-6.8; such drugs would be expected to display poor absorption. Therefore, eccrine sweat glands may act as a route out as well as a route in through the skin. Apocrine glands develop at the pilosebaceous follicle to provide the characteristic regionalised distribution mainly in the skin of the armpits, the areola of the breasts and the perianal region. The secretory portion can be located in the dermis or in the hypodermis (adipose cells). Their excretory ducts open into hair follicles and secretion is more viscous than that of the eccrine glands. This is because the milky or oily secretion contains proteins, lipids, lipoproteins and saccharides, thus, providing a rich environment for bacteria to grow, giving rise to the characteristic body odour (Barry 2001b).

1.2.2.2. Pilosebaceous Follicles

The hair follicle, hair shaft and sebaceous gland collectively form what is termed the pilosebaceous unit. Hair follicles are found over the entire surface of the skin except for the soles of feet, palms of hands and the lips (Figure 1.4). They are skin organs that produce hair. Attached to the follicles are the sebaceous glands, which synthesise and secrete sebum, a solution of neutral, non-polar lipids such as free fatty acids, waxes and triglycerides. Sebum is released into the follicle via tiny ducts adjacent to the hair follicles, from which it spreads over the hair and skin (Lauer et al. 1995). The main role of sebum may be to waterproof the skin and hair, although the exact function of sebum glands is not fully understood and some researchers believe they are merely an evolutionary artefact or may help with the birthing process (Danby 2005). Other hypotheses propose that these glands assist with the three-dimensional organisation of the skin surface lipids and influence follicular differentiation. Sebum also transports fat-soluble antioxidants and may offer protection against ultraviolet light and / or have anti-inflammatory and anti-microbial properties (Zouboulis et al. 2008).

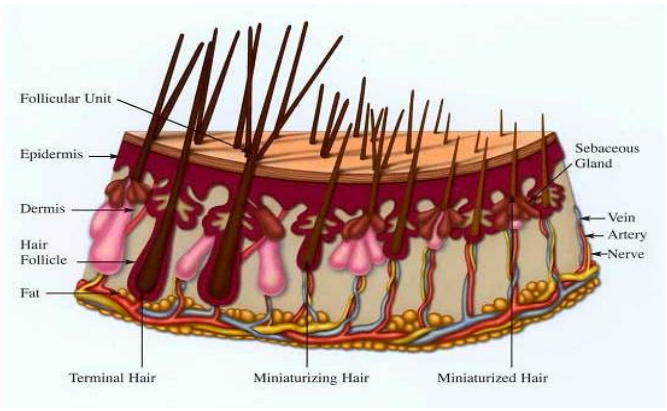


Figure 1.4. Structure of the hair follicles (grayhaircolor: info/youthhair.htm).

1.2.3. Variables in Skin Structure Affecting Percutaneous Absorption

There may be deviations in this basic structure of the skin that can affect the percutaneous absorption of penetrants. Some of these deviations are due to species differences, regional skin site variations, skin age and skin condition variables (Barry 1987a).

1.2.3.1. Species Variation and Age

Despite different species having similar skin structures, they also present some slight differences in their skin composition. For example, they might present a different lipid composition in bilayer lipids and components in corneocytes, or have a different organisation of the components in their skin. These differences will affect the ability of the skin to act as a barrier to foreign material. *In vitro* permeation studies using human skin are limited because of difficulties of procurement, storage, expense and variability in permeation. Animal skin is often more permeable than human skin, since it contains a greater number of hair follicles and lacks sweat glands. Furthermore, age is another factor upon which the penetration of substances depends. It is usually assumed that the skins of fetuses, the young and elderly are more permeable than adult tissue. There are many publications available regarding species differences (Rittirod et al. 1999; McDougal et al. 2000; Magnusson et al. 2001; Andega et al. 2001; Kanikkannan et al. 2001; Ngawhirunpat et al. 2004), but only a few based on age variation (Shah et al. 1992; Kanikkannan et al. 2001; Ngawhirunpat et al. 2001).

1.2.3.2. Anatomical Site

There is inter- and intra-individual variability in skin. Certain regions, such as the face and the scalp, are significantly more permeable than the others. Rougier et al. (1987) have demonstrated that the skin of the human forehead is 2 to 3 times more permeable than that of the arm or abdomen, despite the similarity in the thickness of the stratum corneum in these different sites. The horny layer thickness does not, therefore, appear to be a sufficient explanation of similarities or differences in the absorption of the same molecule from one anatomic site to another in the same species.

1.2.3.3. Temperature and Hydration

A temperature gradient exists across the skin, ranging from typically 32 °C at the skin surface to 37 °C in the blood. *In vivo* permeation studies have demonstrated the influence of temperature on the percutaneous absorption of substances under physiological conditions. The diffusion constant for the movement of a penetrant across a homogenous membrane increases as temperature rises (Clarys et al. 1998). As a result, the penetration of active substances from transdermal drug delivery devices may be affected in a significant way by variations in skin temperature. Hydration increases the permeability of stratum corneum and penetration through hydrated skin is higher than through dry skin. Both temperature and hydration are important factors that should be taken into consideration in the permeability assessment experiments. For

example, it is known that a rise of 10 °C in temperature can produce a two- to three-fold increase in permeation (Franz 1990), with some of the reasons for this effect being outlined in Section 1.6.1. Additionally, the extent of variation of hydration and the mechanisms by which water acts on skin absorption is discussed in Sections 1.5.2 and 1.6.2. Hydration has been shown to increase the permeability of most molecules into the skin. When an occlusive patch is left on the skin, it prevents the loss of water from the surface of the skin (TEWL) resulting in increased water levels within the stratum corneum of up to 50 percent (Blank & Scheuplein 1964).

1.2.3.4. Skin Condition and Disease

The intact skin is a tough barrier but many agents damage it. Vesicants such as acid and alkalis injure barrier cells and, thus, promote penetration, as do cuts, abrasions and dermatitis. Skin diseases generally alter the lipid / protein composition of the stratum corneum and consequently change the barrier function of the skin. After injury or removal of the stratum corneum, the skin builds a temporary barrier that persists until the regenerating epidermis can form keratinised cells. Even the first complete layer of new stratum corneum cells formed over a healing layer can markedly reduce permeation (Barry 2001b). It also has to be mentioned that cellular responses to wound-healing cytokines are preserved as people age. Abnormalities in wound healing in older patients may be the result of altered immune initiation of healing or the cumulative result of concomitant disease (Grasilli et al. 1996).

1.2.3.5. Metabolism

Skin is involved in the metabolism of drugs, including steroids as well as polycyclic aromatic hydrocarbons; the latter are known for their carcinogenic effects. Although skin's metabolic capability is inferior to liver in per mg tissue base, the fact that the skin is one of the largest organs in the body makes it an important drug metabolising organ, whether or not the drug is administered in a topical vehicle or in a transdermal patch.

Table 1.1. Drug metabolism enzyme in the skin (Kao & Carver 1990).

Phase I reactions	Phase II reactions
Hydrolytic reactions: ester hydrolysis, epoxide hydrolysis	*Conjugation reactions:* glutathione conjugation, glucuronic acid conjugation, sulphate conjugation, glycine conjugation
Oxidative reactions: Alcohol oxidation , hydroxylation, deamination, methylation, realkylation	
Reductive reactions: Carbonyl reduction, C=C reduction	

The enzymes mentioned in Table 1.1 are located in the epidermis and dermis. Concentrations of enzymes are higher in the epidermis, whereas the total amount of enzymes is higher in the dermis because of the significantly increased relative mass of the latter. The effective metabolic capability of these two sites is not well defined, since drug molecules may diffuse between the cells (especially the dermis cells) so that they are not taken up and metabolised. The main enzymes responsible for steroidal metabolism are cytochrome P450s. The other major enzyme group is the esterases, which is the reason why many ester prodrugs, which typically have higher permeability across the stratum corneum than their parent compounds, have been developed or investigated for transdermal drug delivery. Effects of skin metabolism on percutaneous penetration of drugs with high lipophilicity were studied *in vitro* using rat skin pretreated with and without an esterase inhibitor, diisopropyl phosphorofluoridate. The results indicated that skin metabolism directly affected the total amount that penetrated in the case of highly lipophilic drugs and it was also found that the higher the metabolic rate of hydrophilic drugs is, the greater the resultant amount that penetrated the skin. Therefore, it was proposed that, when optimal prodrugs are designed for the purpose of enhancing percutaneous penetration, the bioconversion rate to parent drugs as well as the lipophilicity of prodrugs becomes an important consideration (Bando et al.,1997).

1.2.3.6. Vehicle Interactions

A pharmaceutical vehicle may change the physical state and permeability of the skin and consequently, the choice of vehicle is an obvious important consideration. Ideally, the vehicle should not irreversibly affect the barrier properties of the skin. Furthermore, the solubility of the drug in the vehicle, particularly at the extremes of polarity, will predetermine its partitioning between the vehicle and the stratum corneum lipids and, thus, influence dermal kinetics (Howes et al. 1996).

1.2.4. Functions of the Skin

The skin protects the body from physical damage, radiation, infection and chemical attack (extrinsic) and also from loss of fluid, electrolytes and proteins (intrinsic). The hardened surface of dead keratin-rich cells provides a physical barrier to the entry of foreign bodies, bacteria and chemicals. The large number of nerves in the dermis gives the sensation of touch, pressure, heat and pain, enabling the brain to react to danger or pleasure. Sweat has a function in the elimination of some toxic products, drugs and in the secretion of pheromones. It also has a function in temperature control in helping to maintain body temperature at 37 °C. Additionally, water is lost from the body by constant gentle evaporation through the skin. However, it is very important to ensure that excessive water loss is avoided in order to prevent dehydration. Finally, vitamin D is produced in the skin as the result of the action of sunlight on 7-dehydrocholesterol, a fatty compound found in the skin.

1.3. PERMEATION OF TOPICALLY-APPLIED COMPOUNDS THROUGH SKIN

There are two main routes of drug permeation through the skin: transappendageal and transepidermal (Barry 2002). (Figure 1.5) These proposed pathways are not mutually exclusive as there are no active transport mechanisms of the stratum corneum; the molecule will take the path of least resistance often determined by its physicochemical properties (Flynn 2002).

1.3.1. Transappendageal Permeation

Permeating molecules may enter through the hair follicles or sweat glands, which bypass the stratum corneum and extend deep into the dermis. This route is also called the 'shunt route.' It provides a parallel pathway by which solutes can be absorbed by sweat ducts and hair follicles without hindrance by the stratum corneum. The hair follicles and sweat glands have openings that effectively bypass the stratum corneum barrier and reach the underlying dermal structures. The role of appendages in transdermal drug penetration has been controversial, possibly due in part to the relatively sparse hair cover in humans and animals, such as the pig, and the small fraction of total surface area they constitute (Roberts et al. 2002). However, greater amounts of radiolabelled pesticides were recovered from the urine after their application to the scalp – average thickness 5-6 mm (Hori et al. 1972) – in comparison to those attained when applied to the (less hairy) forearm – average thickness of 1 mm (Maibach et al. 1971). In contrast, a different study suggested that transfollicular transport contributed little to the transdermal drug penetration process (Rougier et al. 1987). In contrast, early studies using human skin suggested that a follicular or 'shunt' pathway may be important immediately following topical drug application, but, because of its larger surface area, the intercellular pathway becomes dominant (Scheuplein 1967). The sweat glands are actively secreting fluids and this may counteract any inward diffusion from occurring. Extensive literature reviews show that any transfollicular delivery that does occur is heavily dependent upon properties of the drug (such as size, charge, lipohilicity) and upon the follicular density of the skin surface (Lauer et al. 1995). Whilst there is evidence that large and polar molecules might be transported transappendageally, determining the exact method of transfer is fraught with difficulties, thanks in particular to the absence of suitable experimental models (Barry 2002).

1.3.2. Transepidermal Permeation

As the contribution of the transappendageal route seems limited at best, the transepidermal route is widely regarded as the main pathway for molecules diffusing through the skin. The corneocytes of the stratum corneum are particularly difficult to penetrate, as the cornified envelope prevents the entry of any lipid-soluble agents. Nevertheless, these cells do swell several-fold in the presence of water, indicating a positive reaction when exposed to hydrophilic substances (Bouwstra et al. 2003). Water is present within the lower levels of the epidermis at concentrations of 60% and in the stratum corneum at 20% (Morganti et al. 2001). Water is known to continuously escape outward through the skin in a

phenomenon known as transepidermal water loss (TEWL) designed to maintain aqueous homeostasis (Delgado-Charro & Guy 2001). Therefore, it is believed that water soluble molecules that do permeate though the stratum corneum do so intercellularly. This is a slow route for hydrophilic molecules, but a relatively straightforward one, perhaps occuring via temporary aqueous pores (Sznitowska et al. 1998; Flynn 2002).

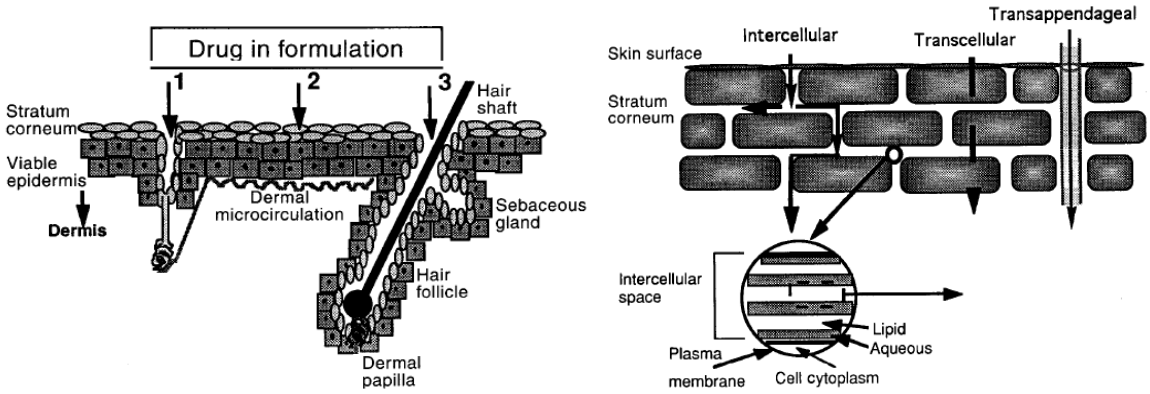


Figure 1.5. Schematic representation of transepidermal (route two) and transappendageal (routes one and three) permeation routes (Hayden et al. 1997; Sznitowska et al. 1998).

As the inner environment of the corneocyte is a hydrophilic one with water bound to the densely-packed keratin network, lipophilic molecules are not thought to partition into these cells upon contact with the stratum corneum. These lipophilic substances can instead be dissolved within the intercellular lipids and this is generally regarded as the pathway by which these types of compounds penetrate the stratum corneum (Yu et al. 2003). Direct microscopic evidence (Bodde et al. 1991) and indirect measurements such as permeability and the lag time of molecular compounds (Potts & Francoeur 1991) lend support to this argument. The intercellular lipids create a highly torturous route that is estimated to be 10 to 50 times greater than the thickness of the stratum corneum itself (Frasch & Barbero 2003). It is also postulated that hydrophilic molecules may be influenced by this route as well, i.e. along the polar head groups of the lipid lamellae, as lipid extraction increases TEWL (Abrams et al.1993; Monteiro-Riviere et al. 2001). Although the location of these aqueous pathways is uncertain, the existence of such pathways to accommodate the diffusion of polar compounds through the stratum corneum has been suggested (Clifford 2002).

Following penetration through the stratum corneum, drugs diffuse across the viable epidermis and dermis and then are transported away by the cutaneous microvasculature. The blood supply is very rich, with a flow rate of 0.05 ml min^{-1} per cm^3 of skin, and reaches to within 0.2 mm of the skin's surface. (Figure 1.6) This blood volume usually functions as a 'sink' with respect to the diffusing molecules, which reach it during the process of percutaneous absorption (Yamashita & Hashida 2003).

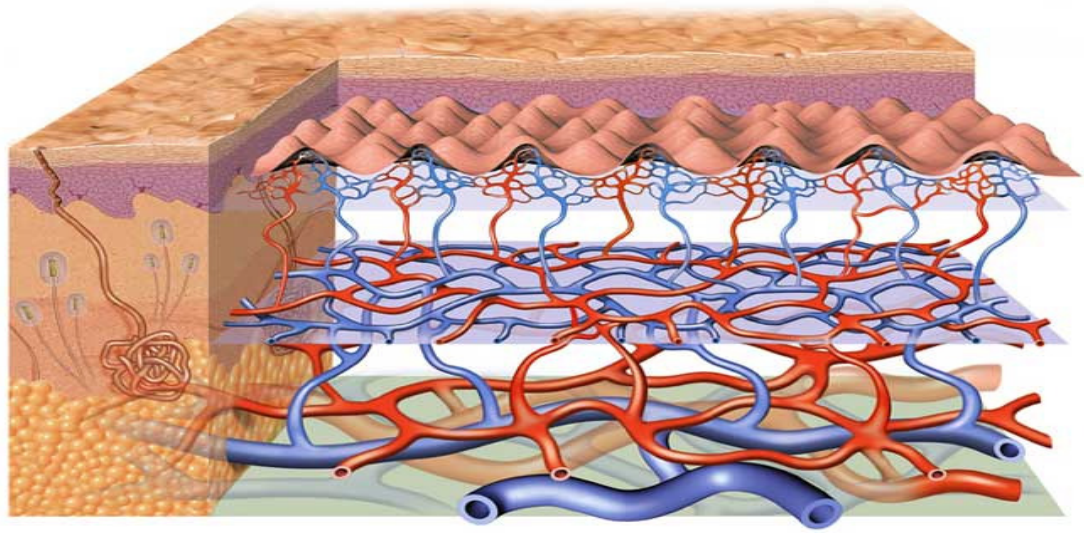


Figure 1.6. Blood supply system (www.scf-online.com/english/40_e/ bloodvessel40_e.htm).

The uptake of molecules into the blood and their subsequent distribution are usually rapid compared to the permeation process, unless the diffusing compound itself constricts the blood vessels and thereby decreases its own clearance. The steady-state plasma levels (C_p) following topical application of a compound can be calculated by the following equation (Equation 1.1):

$$C_p = (A \times K_p \times C_{app}) / Cl \qquad \text{(Equation 1.1)}$$

where A is the area of application, K_p is the permeability constant of the compound, C_{appl} is the applied concentration and Cl the clearance.

1.4. Physicochemical Characteristics of the Penetrants

1.4.1. Permeability Coefficient

The permeability of molecules across a membrane can be expressed with Equation 1.2.

$$K_p = P D / h \qquad \text{(Equation 1.2)}$$

where partition coefficient (P), when the diffusion coefficient (D) and the thickness of the membrane (h).

Graphically, the permeability coefficient (K_p) is expected to be a linear function of the partition coefficient (P) when D and h are constants. Therefore, an increase in K_p can occur by increasing P. An increase in partition coefficient can be achieved by formulating a drug with an affinity for the stratum corneum much greater than that for the vehicle. Still, this approach may result in poor solubility of the drug in the vehicle and, thus, the amount of the drug loaded in the formulation will be insufficient to provide delivery for the length of time required. Thus, a balance between P and C_v must be achieved. The partition coefficient is a measure of the drug's lipophilicity and an indication of its ability to cross cell membranes. Drugs having values of log P greater than 1 are classified as lipophilic, whereas those with less than 1 have been considered as 'hydrophilic' drugs. However, it must be kept in mind that in the case when the permeant is ionisable, the pH of the vehicle and the permeant's ionisation constant, K_a, will determine the actual concentrations of ionised and non-ionised species and, thus, influence the partition coefficient.

1.4.2. Partition Coefficient

Traditionally, lipophilicity is understood as the affinity of a compound or a molecular fragment to a lipidic environment and it is expressed as the logarithm of the partition coefficient (log P) of a solute between two essentially immiscible solvent phases (Caron et al. 1999). When a drug or any other biomolecule is shaken within two immiscible liquids, the molecules are distributed between the two phases in order to achieve a minimum free energy of the system. Thus, the partition coefficient (P) for a compound being separated in an aqueous / organic phase can be defined as the ratio of the concentration in the organic layer divided by its concentration in the aqueous layer. Partition coefficients are obtained as the ratio of the concentration of the species in each phase at equilibrium (Equation 1.3):

$$P = [C]_{organic} / [C]_{aqueous} \qquad \text{(Equation 1.3)}$$

The greater the value of P, the higher the lipid solubility of the solute. It has been shown for several systems that the partition coefficient can be approximated by the solubility of the solute in the organic phase divided by its solubility in the aqueous. Thus, P is a measure of the relative affinities of the solute for an aqueous and a non-aqueous or lipid phase (Attwood 1994). Essentially, the stratum corneum barrier is lipophilic, with the intercellular lipid lamellae forming a conduit through which drugs must diffuse in order to reach the underlying vascular infrastructure and to access ultimately the systemic circulation (Naik et al. 2000). For the above-mentioned reason, lipophilic molecules are better accepted by the stratum corneum. A molecule must first be liberated from the formulation, partition into the uppermost layers of the stratum corneum, diffuse through the entire thickness and then repartition into the more aqueous viable epidermis. Thus, ideally, a drug should possess both lipoidal and aqueous solubilities to be absorbed. If it is too hydrophilic, the molecule might not transfer into the stratum corneum and if it is too lipophilic, the drug could remain in the stratum corneum layers. In general, drugs having a log P value between 0.8 and 3.3 will have reasonable penetration rate through the stratum corneum (Barry 2001a). It has been reported that a parabolic correlation of convex type exists between lipophilicity and the permeability coefficient of drugs and that there exists optimal value for the

partition coefficient of drugs. This parabolic nature of activity versus log P is due to a combination of factors, including protein binding, low solubility and binding to extraneous sites of compounds with high log P values.

1.4.2.1. Intermolecular and Intramolecular Forces

Log P data contain a variety of information about inter- and intramolecular forces affecting partitioning and the resultant biological phenomena (Caron et al. 1999). One approach to describing the intermolecular forces that govern the partitioning of neutral solutes is the so-called 'solvatochromic' equation, which factorises lipophilicity into parameters describing various properties of the solutes (Equation 1.4):

$$\text{Log P} = v V_w + p \Pi^* + a\alpha + b\beta + c \qquad \text{(Equation 1.4)}$$

where V_w is the calculated Van der Waals volume, Π^* , α, β are the solvatochromic parameters (dipolarity, hydrogen bond donor acidity and hydrogen bond acceptor basicity respectively) and v, p ,a and b are the regression coefficients reflecting the contribution of each parameter to log P.

The intermolecular interactions influencing lipophilicity have been classified by Caron et al. (1999) into three main classes: electronic conjugations, interactions involving polar groups and steric and hydrophobic effects.

1.4.2.2. Distribution Coefficient (Log D)

For ionisable compounds, the partition is changed as a function of pH. This relationship is called a distribution constant (log D), or sometimes also called an apparent partition coefficient. Whereas log P describes partition of the unionised (neutral) form of the compound, log D describes the total partition of both ionised and unionised form. Thus, for acidic compounds, log D is decreased as a function of increased pH (acids are more ionised and, thus, more water-soluble in higher pH), while for basic compounds log D value is increased as a function of increased pH (bases are less ionised and, thus, less water soluble in increased pH) (Poda et al. 2001). Often when characterising the compound, log D is studied across the wide pH range.

Log D is related to log P and the pKa by the following equations (Equations 1.5 and 1.6, Scherrer & Howard 1977):

$$\text{for acids } \log D_{(pH)} = \log P - \log (1 + 10^{(pH-pKa)}) \qquad \text{(Equation 1.5)}$$

$$\text{for base } \log D_{(pH)} = \log P - \log (1 + 10^{(pKa-pH)}) \qquad \text{(Equation 1.6)}$$

1.4.3. Fick's Laws of Diffusion

For most chemicals, the main transport mechanism through the skin, as through most other biological membrane barriers of physiological or pharmaceutical relevance, is passive diffusion. Passive diffusion is

the mechanism by which matter moves from one region of a system to another, following random molecular motions. In other words, there is a random walk of an ensemble of molecules from regions of high concentration to regions of lower concentration. The diffusion process can be expressed as Fick's first and second law of diffusion. For a given medium, the particle flux (J), the number of particles traversing through unit perpendicular area in unit time is proportional to the concentration gradient (Silbey & Alberty 2001). This is expressed as Fick's first law of diffusion (Equation 1.7):

$$J = - D \frac{\partial C}{\partial X} \qquad \text{(Equation 1.7)}$$

where J = rate of transfer per unit area of the surface (the flux), C = concentration of the diffusing substance, X = spatial coordinate measured normal to the section, D = diffusion coefficient, or diffusivity.

The proportionality constant in the above equation is the diffusion coefficient (D) of the corresponding medium and the minus sign only indicates that the flow is directed towards smaller concentrations, a direction opposing the concentration gradient. The diffusion coefficient or diffusivity (D) is a rough measure of the ease with which a molecule can move about within a medium, in this case the stratum corneum. Since diffusion through the stratum corneum is passive, large molecules diffuse more slowly than small ones. In general, drugs with a molecular weight (MW) smaller than 500 Da give acceptable permeation rates (Brown et al. 2006). Therefore, the MW of a chemical which is generally a good indicator of its molecular size is related to the diffusion coefficient. However, diffusivity is not only dependent on MW and volume but also on the degree of interaction between the permeant and the stratum corneum. Furthermore, partial derivatives are used because, in the general case, permeant molecule distribution is a function of both time and spatial coordinates. The concentration gradient over the stratum corneum will depend primarily upon chemical characteristics of the permeant including solubility, lipophilicity, ionisation and stability (Smith 1990). The concentration gradient at a time can be given by Equation 1.8.

$$\text{Conc grad.} = (C_v - C_d) \qquad \text{(Equation 1.8)}$$

where C_v = drug concentration in the formulation and C_d = drug concentration on the other side of the membrane.

When a linear concentration gradient has been established, steady-state conditions exist and the flux per unit area (J) of material across the skin is proportional to the concentration gradient (Equation 1.9):

$$J = DK (C_v - C_d) / h \qquad \text{(Equation 1.9)}$$

where K = partition coefficient for the chemical with respect to its distribution between the skin lipids and the formulation and h = thickness of the membrane.

In the steady state situation, the drug concentration in the formulation is constant and sink conditions prevail, i.e. the local concentration (C_d) is much less than the concentration in the formulation (C_v), hence $C_v - C_d \sim C_v$. Therefore, the above equation can be written Equation 1.10 below, which, in turn, is often simplified to Equation 1.11:

$$J = DK C_v / h \qquad \text{(Equation 1.10)}$$

$$J = K_p C_v \qquad \text{(Equation 1.11)}$$

where K_p is the stratum corneum formulation permeability coefficient ($K_p = DK / h$) and relates to the partitioning and diffusion behaviour of the permeant.

When a permeant is placed on the skin surface, it will partition into the lipids and diffuse through the intercellular channels. Following a short period of exposure, there will be a non-linear concentration gradient across the stratum corneum, the shape of which is described by Fick's second law of diffusion. Fick's second law is concerned with concentration gradient changes with time (Equation 1.12):

$$dC / dt = dJ / h \qquad \text{(Equation 1.12)}$$

and, in combination with Equation 1.10, the following Equation 1.13 results:

$$dC / dt = d (DK C_v / h) / h \qquad \text{(Equation 1.13)}$$

Evidence suggests that there is a non-uniform resistance to diffusion, with the outermost lipids being more permeable. The non-steady state conditions give rise to the lag time found when *in vitro* skin diffusion experiments are performed. From Fick's laws, it is easily shown that the lag time (τ or T_{lag}) is related to the diffusion coefficient (D). The lag time is the time obtained from extrapolation of the steady state portion of the graph to the intercept on the time axis (Figure 1.7). Additionally, lag times obtained from permeation experiments with human skin tend to be variable and may include a component arising from interactions between the stratum corneum and the permeant.

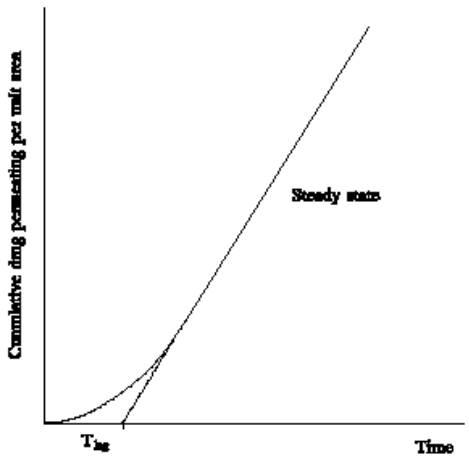


Figure 1.7. Typical permeation profile for a molecule diffusing across human skin.

1.4.4. Molecular Size

The diffusion coefficient of a solute decreases as the solute size increases. With respect to the diffusion coefficient in the stratum corneum, different authors have proposed different functional forms to describe the effect of solute size (Potts & Guy 1992; Kasting et al. 1987). In these functions, the diffusion coefficient decreases exponentially with increasing molecular size.

1.4.5. Ionisation Effect

The pH partition theory is well documented for the general absorption of ionisable drugs across the gastrointestinal tract, but it is less well described in the dermal and transdermal delivery of drugs (Hadgraft & Valenta 2000). One of the most important factors very often ignored in dermal formulation design and in the prediction of skin permeability is that many potential permeants are weak acids or weak bases and will therefore be ionised. The pH within the stratum corneum gradually changes from pH 5 on the surface to pH 7 in the upper viable epidermis. As a consequence of this pH-gradient, often a pH between 4 and 7 will be chosen for the aqueous phase of a dermal formulation. In the innermost stratum corneum layers, a pH of 7 will produce 90% ionisation of the fatty acids and head-group repulsion will be great. At the surface, the pH of 5 will cause almost minimal head-group repulsion, tending to increase crystallinity and promote a bilayer structure (Lieckfeldt & Lee 1995). The total flux (J_{tot}) of a permeant through the skin is a composite term, which can be attributed to transport of both the ionised and unionised moieties. The transport properties can be described by the following Equation 1.14:

$$J_{tot} = (K_{punion} \cdot C_{union}) + (K_{pion} \cdot C_{ion}) \qquad \text{(Equation 1.14)}$$

where K_{punion}, K_{pion} are the permeabilities of the unionised and ionised species respectively and C_{union}, C_{ion} are the respective concentrations. The ambient pH and pKa of the permeant will determine the relative amounts

of ionised and unionised species. According to the pH partition theory, for any given pH and pKa, it is possible to calculate the amounts of C_{union} and C_{ion} (Equations 1.15 and 1.16):

$$pKa - pH = \log (C_{union} / C_{ion}) \quad \text{for acids} \qquad \text{(Equation 1.15)}$$

$$pka - pH = \log (C_{ion} / C_{union}) \quad \text{for bases} \qquad \text{(Equation 1.16)}$$

When considering maximum flux, both drug permeability and aqueous solubility must be considered, since J_{max} is the product of the permeability (directly related to partition coefficient) and the aqueous solubility. For an ionised component, the partition is significantly smaller than that of the unionised species, whereas its aqueous solubility is considerably higher than for the unionised species.

1.5. PHYSICOCHEMICAL CHARACTERISTICS OF THE VEHICLE

1.5.1. Release of Compounds from the Vehicle / Thermodynamic Activity

For maximum penetration rate, the drug should be at its highest thermodynamic activity. The following Equation 1.17 defines the thermodynamic activities of the permeants and shows that flux is predicted to be directly proportional to the thermodynamic activity of the penetrant in the vehicle:

$$J = \alpha D / \gamma h \qquad \text{(Equation 1.17)}$$

where J is the flux of the compound through the barrier, α is the thermodynamic activity of the compound in the donor solution, D is the diffusion coefficient of the compound, γ is the effective activity coefficient of the compound in the membrane, and h is the barrier thickness (Higuchi 1960).

Dissolved molecules in saturated solution are in equilibrium with pure solid (which by definition is at maximum activity for an equilibrated system). Thus, the solute molecules are also at maximum activity. Therefore, all vehicles containing drug as a finely-ground suspension should produce the same penetration rate provided that the systems behave ideally, i.e. D, γ and h remain constant (Barry 2001a). Under ideal conditions all formulations that are saturated with a particular drug will yield the same J_{ss} across the skin. For example, drug X having a solubility of 2 mg ml^{-1} and 20 mg ml^{-1} in vehicles Y and Z respectively will penetrate the skin at an equivalent rate when delivered from saturated formulations in either vehicle, providing that the vehicle does not interact with and modify the membrane in any respect.

A saturated drug formulation can give the maximum C_v possible. However, crystals settle easily in a saturated formulation in response to temperature changes. Polymers may be incorporated to inhibit recrystallisation in unstable supersaturated preparations. During storage, the drug remains entrapped in the polymeric matrix,

whereas during the application, the drug is mobilised by thermodynamic changes in the polymeric structure (thermodynamic freezing). To avoid the risks associated with direct supersaturation, strategies can be employed to ensure supersaturation occurs only at the site after application to the skin (Bracht 1999). For example, these can include:

1. evaporation of a dry solvent from the system,
2. uptake of water from the skin and
3. activation of thermodynamically 'frozen' drug supersaturated islands by hydration.

1.5.2. Effect of Vehicle on the Skin

It should be noted that only a few vehicles are really inert on human skin (Wiechers 1989). Most vehicles in present use show some interaction in one way or another. This can vary from simply occluding the skin (thereby preventing water loss by evaporation, which results in a more hydrated stratum corneum), to extracting lipid components from the stratum corneum (thereby reducing its barrier function). Most vehicle components penetrate the first layers of the stratum corneum to some extent, thereby possibly increasing the drug solubility within these layers but they may also affect drug binding or interact with tissue components on their way through the stratum corneum. Depending on their physicochemical characteristics, the vehicle molecules also follow a distinct route through the skin, which might be different from that of the penetrant. Water is an example of a compound that interacts with the polar head groups of the lipid bilayer resulting in hydration shells via hydrogen bonding. The hydration spheres of the lipids will then be disturbed, which loosens their packing. This results in a more fluid and more permeable hydrophobic route. However, it also results in an extended hydrophilic domain with increased fluidity, which favours the diffusion of polar penetrants.

The term 'penetration enhancer' is applied to materials that have a direct effect on the permeability of the skin barrier. Some materials may act by a direct chemical insult on the skin while others may not have a specific barrier effect. Many solvents enter the stratum corneum, change its solution properties by altering the chemical environment and, thus, increase partitioning of a second molecule into the horny layer. This molecule may be a drug, a coenhancer or a cosolvent. For example, ethanol increases the penetration of nitroglycerin and estradiol (Barry 2001a). Furthermore, surfactants are known to enhance transport of polar drugs via solubilisation and removal of intercellular lipids via interaction and binding to keratin filaments of the intracellular matrix, resulting in disruption of cell order. In contrast to the penetration enhancers above, surfactants have the added property of being able to form micelles and to reduce surface tension. As a result of the similarity in structure of surfactants and membranes, such as the intercellular bilayer in the stratum corneum, adsorption at interfaces readily occurs, leading to a reduction in interfacial tension (Walters 1989). Liposomes have also been addressed as vehicles that might affect skin permeation. They are colloidal particles, mainly made of phospholipids with or without cholesterol, which form concentric biomolecular layers that may entrap drugs to form liposomes. Stratum corneum lipids have been employed with a view to achieving better skin penetration (Gregoriadis 1991).

Alteration in their composition and structure results in vehicles with tailored properties. Flexible and ultradeformable liposomes have been reported, with claims of enhanced transdermal drug delivery to efficiencies comparable with subcutaneous administration (El Maghraby et al. 2008).

1.6. ENVIRONMENTAL PARAMETERS

1.6.1. Effect of Temperature

Skin temperature can have an impact on the rate of penetration of chemicals in two different ways (Bunge & McDougal 2000). First, increasing the temperature of the skin has been shown to increase the rate of penetration by a direct effect in the skin that follows an Arrhenius relationship (Scheuplein & Blank 1971). Secondly, temperature may affect the blood flow to the skin and therefore affect the amount of chemical absorbed. The use of heat as a means of enhancing percutaneous absorption has been documented in the past (Blank et al. 1967), but it has never been fully exploited as a means of helping drug delivery across the skin. Thus, there have been only a few investigations of the effect of temperature on skin permeation compared to other methods of penetration enhancement. An increase in the temperature of the skin and its environment may well provide the potential for reducing the barrier properties of the stratum corneum (Akomeah et al. 2003).

Using skin permeation data, the activation energy (E_a) for each penetrant was calculated at different experimental temperatures, in accordance with the Arrhenius equation as used by Blank et al. (1967) (Equation 1.18):

$$\text{Log } K_p = \log A - E_a 2.303RT \qquad \text{(Equation 1.18)}$$

where T is the absolute temperature (K), A the frequency, factor and R is the molar gas constant.

One of the functions of the stratum corneum is its role as a protective barrier against water loss and hence its role in maintaining body temperature. This very protective function of the stratum corneum also makes it the main hurdle with regards to drug delivery through the skin. Phase behaviour studies of the stratum corneum have shown that the arrangement and the state of the lipid bilayer change with temperature (White et al. 1988; Krilla et al. 1992; Ongpipattanakul et al. 1994). The lipid bilayer of the stratum corneum can exist in crystalline gel, liquid crystalline state or mesomorphic form depending upon temperature. Since the polymorphism of the lipids of the stratum corneum is critically dependent on chemical composition, it is likely that composition changes of its lipids affect the phase behaviour and consequently the barrier properties of the skin.

1.6.2. Effect of Hydration on the Rate of Chemical Penetration

Normal skin is a partially hydrated tissue that maintains a consistent water content of approximately 5 to 15%, regardless of how much the humidity of the environment varies (Blank & Scheuplein 1964). The stratum corneum plays a double role regarding barrier properties by minimising the TEWL and by preventing external ingress due to its extremely high impermeability. The hydration state of the skin affects the permeability of the stratum corneum, thus, percutaneous absorption enhancement may be achieved by simply increasing the water content in the stratum corneum. Skin hydration can be achieved by applying an occlusive vehicle (e.g. an ointment) to the skin (Norman et al. 2005), or by incorporating specific moisturising factors into the vehicle. Hydration can also be obtained by using polymer patch skin delivery systems (Maibach & Hikima 2006). The normal physiological water content of the stratum corneum depends on the balance between water retention and water loss factors of the tissue. A continuous passive diffusion of water occurs from within the body through the stratum corneum and into the environment (TEWL) because of the water concentration gradient in the stratum corneum. Any external factor that binds water in the tissue or retards the evaporation of water from the skin surface will result in a hypernormal hydration of the stratum corneum. This hydration is associated with a swelling of the corneocytes and an increase in the water content of the intercorneocyte lipid bilayers. Both of these phenomena appear to facilitate xenobiotic delivery across the tissue in a totally reversible manner. The predominant effect of total or partial skin occlusion with, for example, non-aqueous ointment formulations or impervious (non-sorbing) plastic films is increased hydration of the stratum corneum. Swelling of the corneocytes and uptake of water into intercellular lipid domains occurs, often increasing the water content of the stratum corneum by up to 50%. Furthermore, occlusion of the dosed skin prevents loss of the surface-deposited chemical by friction or by exfoliation and thereby topical delivery may be increased. Hydration by occlusive systems or topical vehicles is still the most facile way to obtain a reduction in barrier potential of the stratum corneum and an increase in the percutaneous absorption.

1.7. *IN VITRO* MODELS FOR DERMAL PERMEATION

1.7.1. Introduction

In vitro methods measure the diffusion of chemicals into and across skin to a fluid reservoir and can utilise non-viable skin to measure diffusion only, or fresh, metabolically-active skin to simultaneously measure diffusion and skin metabolism (OECD 2004a). Diffusion across the non-living outer layer of skin, the stratum corneum, is normally the rate-limiting step for percutaneous absorption (Dugard & Scott 1984; Dugard et al. 1984). There are many complex interactions, which may occur during the movement of molecules from the outer layer of the skin into the systemic circulation. There have been numerous attempts to produce simple models of these processes, which have resulted in the development of

various types of *in vitro* systems. There is an urgent need for the further development, evaluation and use of appropriate and reliable *in vitro* methods, since there is increasing pressure on the industry to reduce the number of animals used in safety testing. The *in vitro* approach is a rational one and is based on a mechanistic understanding of the dermal penetration process. Since the skin is a passive barrier, its barrier function is maintained *in vitro*. Moreover, the *in vitro* technology provides direct estimates of penetration without the distorting influence of the rest of the body.

Recommendations on *in vitro* methodologies have been collated as guidelines by regulatory bodies. The FDA Scale-Up and Post Approval Changes (SUPAC-SS) and the International Pharmaceutical Federation in collaboration with the American Association of Pharmaceutical Sciences (FIP / AAPS) have guidelines requiring the performance of release testing from semisolid dosage forms after formulation changes (SUPAC Guidelines 1997; Siewert et al. 2003). In particular, *in vitro* dissolution of pre- and post-change formulations must be compared whenever changes are made to the composition of the product, manufacturing equipment, or process (Liebenberg et al. 2004; Moore & Flanner 1996). Although the FDA SUPAC-SS guidance includes general methodology and incorporates descriptions of diffusion systems, it does not specify a particular test methodology because no compendial apparatus, procedures or requirement for *in vitro* release testing of semisolids topical dosage forms have been described in relevant Pharmacopoeias to date (SUPAC Guidelines 1997; Siewert et al. 2003, Liebenberg et al. 2004).

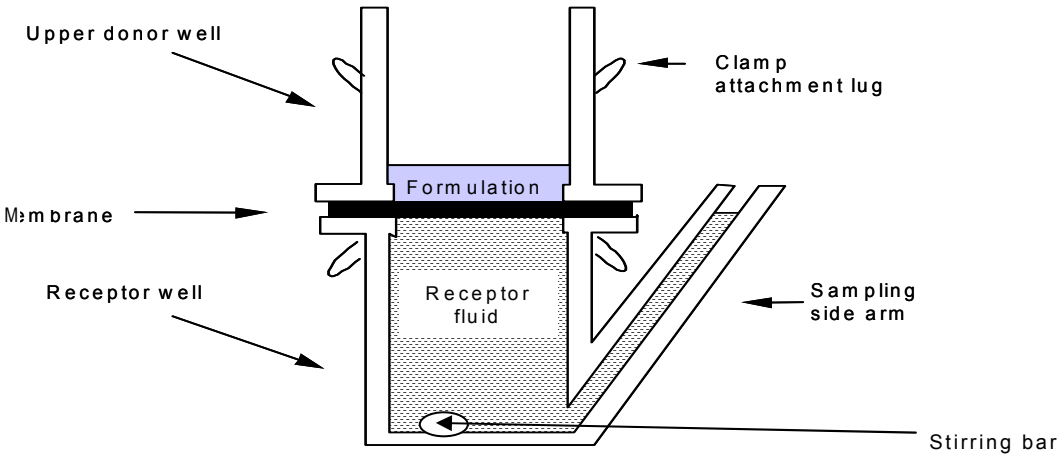


Figure 1.8. Schematic representation of a Franz diffusion cell.

In vitro studies serve as a preliminary phase of drug development to screen for potential candidates that can be included in further studies. *In vitro* data can also be extrapolated into *in vivo* to predict the effect of a drug inside the body. However, *in vitro* studies do not provide pharmacokinetic data and there is also the difficulty of obtaining human skin in sufficient quantities. Briefly, all *in vitro* methods involve separating some portion of the skin from the rest of the animal. Human skin for example can be obtained from a variety of sources by anatomical location and can be presented in a number of different thicknesses. As shown in Figure 1.8, the skin is mounted in a diffusion

cell to allow it to be dosed with the compound of interest on its epidermal surface and to allow the receptor solution under the skin to be sampled. Any *in vitro* protocols used should clearly define the scientific rational for the conditions used and should indicate the limitations of the data with regard to their interpretation. It is critical that all *in vitro* methods have successfully undergone rigorous scientific validation. Many general models of predicting skin permeability (as opposed to 'local' models developed in one laboratory) are produced from data which have been compiled from different sources and which have been generated in different laboratories. Where there is more than one source of K_p value for the same chemical, substantial differences in the resulting permeability coefficients are observed. Nonetheless, the majority of researchers, such as Potts & Guy (1992), comment that 'the scale of variance observed is acceptable and within the expected range of variability for skin delivery experiments.' Such variance is therefore translated into any models subsequently derived and this may be incorporated into and then reflected in the statistical validity and accuracy of the model (Moss et al. 2002).

1.7.2. Membrane Selection

In vitro methods can be developed both with and without a rate-limiting membrane. In the case of the presence of a rate-limiting membrane, the most appropriate membrane for permeation studies is human skin. However, there are a number of practical disadvantages associated with the use of human skin. For example, frozen cadaver skin has been used, which can be very variable in condition and have different permeability properties due to variations in gender, race, anatomical site, age and skin condition of the donor. Viable human skin from plastic surgery can be employed, but unfortunately, such skin is in extremely short supply and is impractical for use in routine dermal penetration studies (Wilshut et al. 1995). Therefore, many *in vitro* permeation studies have used animal skin rather than human as a rate-limiting membrane. A large number of different animal skins have been tested as possible models for human skin, such as hairless mouse, rabbit, guinea pig, rat, pig or shed snake skin. The hairless mouse is used predominantly because it is conveniently economical, attainable, easy to house and hairless. Nevetheless, the permeability and the lipid composition are very different to those found in human cadaver skin; for example, hairless mouse skin has been found to have a 30 to 40-fold higher permeability (El-Kattan et al. 2000). Weanling pig skin is recognised as the closest alternative to human skin in its permeability and lipid composition (Mbah et al. 2011). The criterion for selection of an animal skin should be the correlation between permeation rates using human skin and animal skin. Another alternative for human skin is the use of polymeric membranes and other artificial membranes, such as silastic (polymethyl silicone), cellulose acetate or polyurethane. Yet, permeabilities cannot be predicted adequately from the synthetic membrane data, due to the inherent complexities of skin. Such synthetic membranes showed higher permeation relative to animal and human skin (El-Kattan et al. 2000). Living skin equivalent models (LSEs) have also been employed to assess percutaneous absorption (Hager et al. 1994; Nemecek & Dayan 1999; Kremer et al. 2000). They consist of skin membranes including, for example, reconstituted epidermis, grown in tissue culture and employed as alternatives to animal tissues. Yet, these cultured tissues are generally weaker in mechanical properties and provide less substantial diffusion barriers.

1.7.3. Skin Permeation Apparatus

The permeation rate of the drug across the skin has been measured using several different kinds of *in vitro* skin permeation apparatus. A typical one is composed of 3 main components. The first is the donor compartment (donor vehicle), where the drug is applied uniformly. The second one is the permeation barrier or membrane (i.e. skin), through which the drug passes to the third compartment, the receptor solution. The nature and composition of those donor and receptor components are reviewed below:

Donor solution: If the permeant is dissolved or dispersed in a vehicle, it must diffuse through that vehicle to the skin surface before it can be absorbed. The vehicle can influence the release of the permeant from the vehicle and may interact with the stratum corneum. Factors that affect drug release include the physicochemical properties of the vehicle as well as the properties of the drug and vehicle together. The interaction of the vehicle with the stratum corneum may vary from simply occluding the skin to extracting lipid components from the stratum corneum.

Receptor solution: The receptor solution used in diffusion cells should not only act as an acceptor for permeating drugs, but should provide the water, biochemicals and ions needed for the skin membrane to function in the permeation experiment at the proper pH and osmotic strength (Smith 1990). Often this is physiological saline, Ringer's solution, or some other physiological relevant solution. Other important properties of the receptor solution that have significant effect on drug permeation through the skin are temperature, solubility and stirring (Skelly et al. 1987). Control of the receptor solution temperature is important to minimise variations in experimental conditions. The temperature should be kept at normal physiological conditions, since temperature evaluation may lead to increased hydration of the skin. It is known that a rise of 10 °C in temperature can produce a two- to three-fold increase in permeation (Frantz 1990). Typically, physiological saline or a phosphate-buffered solution maintained at 37 °C is used. This will keep the skin surface at approximately 32 °C, which simulates the temperature of the human skin (El-Kattan et al. 2000). Different cell designs will require different water bath or heated block temperatures to ensure that the skin is at its physiological norm. It is necessary to ensure adequate hydration of the skin particularly if the preparation is to be maintained for more than just a few hours. Solubility (in order to maintain sink conditions) and stirring are also important to allow the permeant to be taken up and transported away from the skin after it has passed through, avoiding a concentration build-up within or below the skin. A homogenous receptor solution can be obtained by stirring the solution. The concentration of the permeant in the receptor solution should remain low, compared with its solubility in the solution, to prevent significant back diffusion. In general, the thermodynamic activity should never exceed 10% of that in the donor formulation to maintain an adequate diffusion gradient (Howes et al. 1996) and such criteria are generally regarded as providing 'sink conditions.'

Penetrant concentration is determined *in vitro* by measurement of the concentration in the receptor or donor chambers at given time intervals, yielding information concerning the steady-state flux and lag times of penetrants. The penetrants may be quantified by instrumental analysis, including chromatography, UV, visible and fluorescence detection and by scintillation counting and specific assays. One of the most

significant issues with the use of non-radiolabelled techniques such as HPLC in cosmetic research groups is that material being delivered can, in the case of, for example, triglyceride-containing, natural oils found in some skincare products, or proteins, be very similar to constituents of the skin tissue and may, thus, be difficult or impossible to differentiate from the sample background (Moss et al. 2002).

There are several *in vitro* models used for the evaluation of drug permeation across the skin. These include the Franz diffusion cell (Figure 1.8), the horizontal-type skin permeation system and the flow-through diffusion cell. The solubility of the drug in the receptor fluid department determines the diffusion cell apparatus to be used. The horizontal-type skin cell is divided into receptor and donor compartments with a low solution volume for each compartment and a small membrane area. The compartments are continuously stirred by a matched set of star-head magnets and the system is temperature controlled by circulated thermostated water through a surrounding water jacket (El-Kattan et al. 2000). Another widely used static system is the Franz diffusion cell (Figure 1.8). It is composed of two compartments, the donor and the static receptor solution reservoir with a side-arm sampling port. The skin is positioned between the two cell halves which together comprise a glass chamber. The two compartments are often held together with a clamp. The temperature in the bulk of the solution is maintained by circulating thermostated water through a water jacket, which surrounds the receptor compartment. During the course of an experiment, small volumes are withdrawn from the stirred receptor solution for the analysis and the receptor compartment is refilled with receptor solution to keep the volume of solution constant during the experiment. Flow-through diffusion cells have also been utilised, which can provide automatic replacement of the receptor solution. As a result, the flow-through cell represents conditions more similar to those encountered *in vivo* because the entire contents of the receptor compartment are replaced on a continuous basis. Such cells can be used with drugs having a lower solubility in the receptor compartment. Nevertheless, since the receptor fluid is continuously renewed, although sink conditions are easily maintained, the large volume of receptor fluid can result in drug concentrations being diluted below the limit of detection.

In order to measure percutaneous absorption *in vitro* several parameters have to be defined or selected. These include the type of skin membrane, the diffusion cell, the receptor fluid, the temperature and humidity, the skin integrity, the means by which the test chemical is applied, the duration of the experiment and the dose and volume of the test chemical. The applied dose can be infinite or finite. An infinite dose experiment requires the application of sufficient drug such that little depletion occurs from the donor phase during the monitoring phase of the study. In contrast, a finite dose study entails the application of an amount that might be typically applied *in vivo*, i.e. the dose of drug applied can become depleted during the study interval. The main skin absorption parameters determined in an infinite dose study are the steady-state flux and the permeability coefficient, as opposed to finite dose studies where the maximum absorption rate may either be reached for some of the time but not be maintained or may not be achieved at all (OECD 2004a). The amount of chemical applied may be very small or very high. As mentioned, the dose applied should mimic the 'in-use' conditions. It should be given as an appropriate volume spread on the skin surface (Howes et al. 1996).

1.7.4. *In Silico* Models Used for the Prediction of Dermal Absorption

Recently, there has been much interest in mathematical models and numerical methods available to predict dermal absorption *in silico* in order to avoid unnecessary and costly *in vitro* and *in vivo* testing. Such models may provide a means of avoiding ethical difficulties with respect to the supply of human and animal skin. Furthermore, increasingly strict legislation on the risk assessment of industrial chemicals (e.g. proposed new European chemicals strategy: Registration, Evaluation, Authorisation and Restriction of Chemicals, or REACH) results in rising costs and increasing time considerations, which can be avoided. Quantitative Structure-Property Relationships (QSPR) have been applied for decades in the development of new drugs. Scientists have been tempted, especially in the pharmaceutical arena, to find the most promising compounds, by investigating relationships of molecular parameters with physicochemical and pharmaceutical properties. QSPR studies have meant that, once a correlation between structure and property is found, it is possible to screen any number of compounds, including those that have not been yet synthesised, using a computer with a view to selecting chemical structures with the desired properties. However, certain limitations to the application of QSPR studies have been identified. For example, they are still not appropriate for the description of some important interactions, such as the membrane partitioning of drug properties, the strength of hydrogen bonds, the influence of desolvation energies on drug-receptor affinities and steric interactions with a (most often unknown) binding site (Grover et al. 2000). Furthermore, the quality of data upon which QSPRs are developed has been questioned (Moss et al. 2002) and this is discussed further in Sections 1.8.4, 1.8.5, 2.1.1 and 2.1.2.

1.8. QUANTITATIVE STRUCTURE - PROPERTY RELATIONSHIPS (QSPRS)

1.8.1. QSPRs Used in the Prediction of Skin Absorption

Many QSPRs have been established to predict percutaneous penetration based on the physicochemical properties of the penetrant and its vehicle. Many of these models reveal a linear relationship with lipophilicity where increasing lipophilicity is associated with increasing skin permeation. Some models also reveal a parabolic relationship with lipophilicity, particularly where there are certain compounds in the group that are highly hydrophobic (Moss et al. 2002). QSPRs are often derived using parameters that are themselves calculated from other QSPRs. For example, the octanol / water partition coefficient P_{ow} has often been used as an input parameter to QSPR equations. In certain cases P_{ow} has been measured for some chemicals, but there are times were a Quantitative Structure - Activity Relationship (QSAR) prediction is used instead. Various software programs can also provide differing estimates for P_{ow} and solute solubility. For a QSPR, the data should be consistent, produced from standardised experimental procedures and obtained for the penetration of the compound through skin, which of course depends on the structure of the skin selected for study (Jones et al. 2004). The dermal absorption measurement that has been most widely used in QSPR modelling is the permeability coefficient K_p, because it characterises the ratio of steady-state flux and the concentration of the test compound (Wilkinson & Williams 2002). There is probably an almost linear relationship for many chemical substances between the applied concentration and the dermally-penetrated amount. However, K_p values should

remain constant by ensuring that the applied concentration of test compound results in a constant flux during most of the monitored diffusion period. Generally, it is accepted that the permeability coefficient is a more reliable parameter than the flux to describe the extent of a dermal absorption potential of chemical substances. K_p is generally constant over a range of concentrations and can be calculated for other concentrations than those used in the experiment (EPA 1992; Fitzpatrick et al. 2004; Potts & Guy 1992).

1.8.2. Historical Overview of QSPRs

1.8.2.1. Brown and Rossi (1989)

The model developed by Brown and Rossi is relatively simple. It assumes only the stratum corneum as a lipophilic barrier and it does not take a dependence on MW into account. Two equations (Equations 1.19 and 1.20) were established from the study of 39 compounds.

$$K_p\ (cmh^{-1}) = 0.1\ [P_{ow}{}^{0.75} / (120 + P_{ow}{}^{0.75})] \quad \text{(Equation 1.19)}$$

$$I = C_w \times A \times T \times 0.2\ [P_{ow}{}^{0.75} / (120 + P_{ow}{}^{0.75})] \quad \text{(Equation 1.20)}$$

where I is the dermally absorbed intake (mg), C_w is the concentration of the chemical in water ($mgcm^{-3}$), A is the area of skin exposed (cm^2), T is the duration of exposure (h) and P_{ow} is the octanol / water partition coefficient

1.8.2.2. The Flynn (1990) Dataset and Subsequent Analyses

Flynn (1990) proposed a number of QSPRs to predict K_p, which stated that very hydrophilic and very hydrophobic compounds had low and high skin permeability, respectively, and that different P_{ow}-dependent QSPRs could be used to predict skin permeability for high and low molecular weight compounds.

1.8.2.2.1. Potts and Guy (1992)

Potts and Guy effectively quantified the approach by Flynn. They proposed a two-parameter model to describe the permeability coefficients of organic compounds through excised skin *in vitro*. They demonstrated the use of log P_{ow} in combination with either MW or molecular volume to predict K_p data (in units of cmh^{-1}) collected by Flynn (1990) (Equation 1.21):

$$\text{Log } K_p\ (cmh^{-1}) = 0.71 \log P_{ow} - 0.0061\ MW - 6.3. \quad \text{(Equation 1.21)}$$

N = 93; R^2 = 0.67; S not reported; F not reported

where N is the number of observations or number of compounds, R^2 is the correlation coefficient, S is the standard error of the estimate and F is Fisher's statistic.

Potts and Guy (1992) did not perform a full statistical analysis on the dataset. Although both descriptors used in the above equation (MW, log P_{ow}) are statistically significant, the statistical fit of the equation is comparatively poor (Moss et al. 2002). Potts and Guy (1992) did observe that up to a 30% variability in the experimental data was to be expected.

1.8.2.2.2. Fiserova-Bergerova et al. (1990)

The model of Fiserova-Bergerova et al. considers the permeation through the protein fraction and the lipid fraction of the stratum corneum separately. However, it fails to predict skin permeation for highly lipophilic compounds because it neglects permeation through the watery epidermal layers. The model is described by the following Equation 1.22:

$$Fl = (c_{sat} / 15) (0.038 + 0.153P) e^{-0.016\,MW} \quad \text{(Equation 1.22)}$$

where Fl: flux ($mgcm^{-2}h^{-1}$), C_{sat} : the saturated concentration of a compound in the vehicle ($mgml^{-1}$).

Even though this model includes MW as an independent parameter, it assumes a similar influence of MW on diffusivity in the lipid and in the protein fraction of the stratum corneum.

1.8.2.2.3. El Tayar et al. (1991)

El Tayar and coworkers (1991) examined various subsets from the Flynn dataset and confirmed the role of hydrophobicity in controlling skin permeability in a variety of these. By using Equation 1.23, they also described a correlation with the partition coefficient of octanol / water solvent system minus the partition coefficient of the heptane-water solvent system (Δ log $P_{ow\text{-}hep}$).

$$\text{Log } K_p\ (cmh^{-1}) = -1.36\ \Delta \log P_{ow\text{-}hep} - 3.38 \quad \text{(Equation 1.23)}$$

$N = 21$, $R^2 = 0.901$, $S = 0.498$.

The heptane-water solute system is a measure of the hydrogen bond donor acidity of the solutes. El Tayar et al. (1991) showed that Δ log $P_{ow\text{-}hep}$ is a more successful approach than the log P_{ow} parameter in correlating molecular properties with skin permeation data. These workers also suggested that MW was not important in the prediction of skin permeability.

1.8.2.2.4. Lien and Gao (1995)

Lien and Gao analysed a subset of the Flynn dataset, which included non-electrolytes, as well as steroid structures. They reported that the number of hydrogen bonds that may be formed by a compound (Hb) could also be taken into account when modelling skin permeability. They proposed the following Equation 1.24:

$\text{Log } K_p \text{ (cmh}^{-1}) = 0.84 \log P_{ow} - 0.07 (\log P_{ow})^2 - 0.27Hb - 1.84 \log MW + 4.388$ (Equation 1. 24)

$N = 22, R^2 = 0.96, S = 0.30, F = 93.6$

where S is the standard error of the estimate and F is Fisher's statistic.

The values of S and F both indicate that the model above is clearly at the limit of statistical validity in terms of the number of variables included to the observations, although it does introduce the possibility of the importance of hydrogen bonding to the diffusive process.

1.8.2.2.5. Barratt (1995b)

Barratt analysed the complete Flynn dataset. He noted that within the dataset, a subset of hydrocortisone derivatives were modelled consistently poorly. Barratt (1995b) extended the Potts and Guy (1992) approach and he derived an improved model for the prediction of permeability coefficients by the inclusion of the melting point as an independent variable. Melting point is a physicochemical property highly dependent upon hydrogen bonding, so the importance of hydrogen bonding to model skin permeability was further emphasised. The most significant equation reported by Barratt (1995b) was for a subset of 60 'small molecules and steroids' (Equation 1.25):

$\text{Log } K_p \text{ (cmh}^{-1}) = 0.82 \log P_{ow} - 0.0093MW - 0.039MPt - 2.36$ (Equation 1.25)

$N = 60, R^2 = 0.90, S = 0.39, F = 176$

1.8.2.2.6. Potts and Guy (1995)

Potts and Guy (1995) attempted to describe the effects of hydrogen bonding, molecular volume (in cm^3/mole) and descriptors for the solute hydrogen bond acidity ($\sum\alpha_2^H$) and the solute hydrogen bond basicity ($\sum\beta_2^H$) on skin permeability by using Equation 1.26:

$\text{Log } K_p \text{ (cmh}^{-1}) = 0.0256MV - 1.72 \sum\alpha_2^H - 3.93\sum\beta_2^H - 4.85$ (Equation 1.26)

$N = 37, R^2 = 0.94, F = 165$

1.8.2.2.7. Abraham et al. (1995)

According to Abraham et al. (1995), molecules can interact with their environment through a variety of intermolecular forces. Abraham et al. calculated the effect of hydrogen bonding on K_p and also indicated the importance of molecular size and hydrogen bonding as predictive tools. By including the use of solvatochromic parameters, Abraham et al. reported similar results to Potts & Guy (1995) and confirmed the importance of hydrogen bonding (Equation 1.27).

$$\text{Log } K_p \text{ (cmh}^{-1}) = -5.33 - 0.62\ \pi_2^H - 0.38\ \sum\alpha_2^H - 3.34\ \sum\beta_2^H + 1.85\ Vx \quad \text{(Equation 1.27)}$$

$N = 22$, $R^2 = 0.978$, $S = 0.268$ and $F = 93.7$

where $\sum\alpha_2^H$: hydrogen bonding donor ability, $\sum\beta_2^H$: hydrogen bonding acceptor ability, Vx : molar volume

The most important factors in controlling the permeability of compounds are hydrogen bonding basicity (which favours water) as well as the size of the compounds (which favours the stratum corneum). In a later study, Abraham et al. (1999) considered the issue of 'outliers' and produced an equation based on a slightly expanded dataset for the prediction of skin permeability (Equation 1.28). However, this model indicated that there might be problems with the permeability coefficients of some compounds, especially steroids.

$$\text{Log } K_p \text{ (cmh}^{-1}) = 0.44\ R_2 - 0.49\ \pi_2^H - 1.48\sum\alpha_2^H - 3.44\ \sum\beta_2^H + 1.94\ Vx - 5.13 \quad \text{(Equation 1.28)}$$

$N = 53$, $R^2 = 0.96$, $S = 0.21$, $F = 213$

where R_2 is the excess molar refraction, $\sum\alpha_2^H$ is the hydrogen bonding donor ability, $\sum\beta_2^H$ is the hydrogen bonding acceptor ability and Vx is the molar volume.

1.8.2.2.8. Robinson et al. model (Wilshut et al. 1995)

According to the Robinson et al. model, the influence of the MW on the permeation coefficient is considered separately for the lipid and protein fraction of the stratum corneum and for the watery layer of the epidermis, which is located beneath the stratum corneum. Accordingly, Equations 1.29 - 1.32 were developed:

$$K_p \text{ (cmh}^{-1}) = \frac{1}{\frac{1}{K_{psc} + K_{pol}} + \frac{1}{K_{aq}}} \quad \text{(Equation 1.29)}$$

where K_{psc} is the permeation coefficient of lipid fraction of stratum corneum, K_{pol} is the permeation coefficient of the protein fraction of stratum corneum and K_{aq} is the permeation coefficient of watery epidermal layer.

$$\text{Log } K_{psc} = -1.326 + 0.6097 \times \log P_{ow} - 0.1786 \times MW^{0.5} \quad \text{(Equation 1.30)}$$

$$K_{pol} = \frac{0.0001519}{\sqrt{MW}} \quad \text{(Equation 1.31)}$$

$$K_{aq} = \frac{2.5}{\sqrt{MW}} \quad \text{(Equation 1.32)}$$

The revised Robinson et al. (1995) model was found to have a residual variance of 0.51 (n = 119).

1.8.2.2.9. Pugh et al. (1996)

Pugh et al. (1996) also addressed the issue of hydrogen bonding and molecular size in skin permeation. According to the Pugh et al. model, diffusion across the stratum corneum depends on H-bonding groups in the penetrant and its MW. For monofunctional compounds (Equation 1.33):

$$\text{Log } (D / h) = -1.67 - 0.756\alpha - 0.741\beta - 0.00578MW \quad \text{(Equation 1.33)}$$

$N = 53$, $R^2 = 0.91$, $S = 0.25$

where D is the diffusion coefficient, h is the thickness of the membrane, α is the H-bond donor and β the H-bond acceptor.

The characteristic α and β values of the various chemical groups imply that each group has a characteristic retardant effect on diffusion. This was termed 'the retardation coefficient' (RC). RC depends on interaction of the H-bonding groups of the penetrant with those of the stratum corneum. Therefore, by knowing RC and α and β for the penetrant, the relative H-bonding can be estimated. However, in another study, Pugh et al. (1998) cast doubt concerning the hydrogen bond donor ability of the compounds he collected and concluded that the stratum corneum was predominantly a hydrogen bond donor. These contradictory results suggest not only the difficulties in data interpretation, but also the difficulty in quantifying and describing hydrogen bonding. A later study by Pugh et al. (2000) demonstrated the usefulness of calculated molecular charges as descriptors of hydrogen bonding, as opposed to the Abraham linear free - energy relationship (LFER) type parameters.

1.8.2.3. Other Datasets and Subsequent Analyses

A larger database of 114 skin permeability values was prepared by Kirchner et al. (1997) from the Flynn (1990) dataset (51 chemicals), together with additional data from regulatory reports from Health Canada. Yet, data for 56 of the additional 63 chemicals employed calculated permeability values other than those that had been experimentally derived (Poda et al. 2001; Frasch & Landsittel 2002; Walker & Comber 2003). Nevertheless, Cronin et al. (1999) analysed the Kirchner et al. (1997) database without acknowledging any awareness of this difference.

1.8.2.3.1. Cronin et al. (1999)

As indicated, the data assembled by Kirchner et al. (1997) were reanalysed by Cronin et al. (1999) in an attempt to develop a more accurate QSPR model (Equation 1.34).

$$\text{Log } K_p \text{ (cmh}^{-1}) = 0.77 \log P_{ow} - 0.0103MW - 2.33 \qquad \text{(Equation 1.34)}$$

$N = 107$, $R^2 = 0.86$, $S = 0.39$, $F = 317$

Percutaneous absorption across excised human skin *in vitro*, according to Cronin et al. (1999), is governed by hydrophobicity and molecular size as proposed previously by Potts and Guy (1992). However, the model obtained in this study has an improved correlation coefficient over that developed by Potts and Guy (1992).

1.8.2.4. Other QSPRs Used for Prediction

1.8.2.4.1. Lipinski et al. (2001)

It was reported that excessive numbers of hydrogen bond donor groups impair permeability across a membrane bilayer. Hydrogen donor ability can be measured indirectly by the partition coefficient between strongly-hydrogen-bonding solvents like water or ethylene glycol and a non-hydrogen-bond-accepting solvent like a hydrocarbon (Paterson et al. 1994) or as the log of the ratio of octanol to hydrocarbon partitioning. Computationally, hydrogen donor ability differences can be expressed by the solvatochromic α parameter of a donor group with perhaps a steric modifier to allow for the interactions between donor and acceptor moieties. The 'rule of 5' is implemented by Lipinski et al. for new compounds synthesised in laboratories and it is based on a distribution of calculated properties among several thousand drugs. If two parameters are out of range, a poor absorption or permeability is possible and, therefore, some drugs will lie by definition outside the parameter cut offs in the rule. The 'rule of 5' states that poor absorption or permeation is more likely when:

1. There are more than 5 H-bond donors (expressed as the sum of OHs and NHs)
2. The MW is over 500 Da
3. The log P is over 5
4. There are more than 10 H-bond acceptors (expressed as the sum of Ns and Os)
5. Compound classes that are substrates for biological transporters are exceptions to the rule.

1.8.2.4.2. Agatonovic-Kustrin et al. (2001)

Artificial Neural Network (ANN) analysis was used to predict the skin permeability of selected xenobiotics. ANN is a mathematical or computational model that is inspired by the structure and / or the functional aspects

of biological neural networks. A neural network consists of an interconnected group of artificial neurals and it possesses information. Neural networks are employed to model complex relationships between inputs and outputs in order to find patterns in data (Bishop 1995) and will be further discussed later on. Permeability coefficients were obtained from various literature sources. A previously reported equation, which was shown to be useful in the prediction of skin permeability, used the partial charges of the penetrants, their MW and their calculated octanol / water partition coefficient. The equation was used to predict the skin permeability for the set of 40 compounds. A successful ANN was developed and the ANN produced log K_p values that correlated well with the experimental ones.

1.8.2.4.3. Moss and Cronin (2002)

Moss and Cronin (2002) developed the model of Potts and Guy (1992) by evaluating the role of steroids in the dataset. Specifically, certain steroids had been observed to be outliers to QSPRs for skin permeability. However, many of the historical skin permeability data for these compounds were found to be inconsistent with more recently acquired data. As a result, Moss and Cronin (2002) reanalysed the QSPRs by replacing the originally published steroid permeability data with those from more recent studies. A highly significant QSPR describing skin permeability in terms of the octanol - water partition coefficient (log P) and molecular weight (MW) was derived (Equation 1.35):

$$\text{Log } K_p = 0.74 \log P - 0.0091MW - 2.39 \qquad \text{(Equation 1.35)}$$

$N = 116$, $R^2 = 0.82$, $S = 0.42$

1.8.2.4.4. Pannier et al. (2003)

Phenomena to be modelled are complex and often riddled with uncertainty in the form of ambiguity. Traditionally, uncertainty is described in mathematical models by random characteristics, but fuzzy set theory allows this uncertainty to be represented through possibility rather than probability (Ross 1995). Three fuzzy inference models were developed using subtractive clustering to define natural structures within the data and assign subsequent rules. All databases produced fuzzy inference models that successfully predicted skin permeability coefficients, with correlation coefficients ranging from 0.83 to 0.97 (Pannier et al. 2003). The lowest correlation coefficient resulted from a model using log octanol / water partition coefficient and MW as inputs with two input membership functions evaluated by two fuzzy rules imposed by the modeller. The correlation coefficient of 0.97 occurred when log octanol / water partition coefficient and hydrogen bond donor activity were used as inputs with three input membership functions evaluated by three fuzzy rules. Fuzzy rule-based models are a realistic and promising tool that can be used to model and predict successfully skin permeability coefficients.

1.8.2.4.5. Mitragotri (2003)

Mitragotri tried to compile fundamentally-based analytical expressions that could be used to predict skin permeability for hydrophilic as well as hydrophobic solutes. Solute permeation through four possible routes in the stratum corneum (i.e. free-volume diffusion through lipid bilayers, lateral diffusion among lipid bilayers, diffusion through pores and diffusion through shunts) was analysed. The first mode included solute diffusion through lipid bilayers by hopping between free volume pockets. This mode is particularly important for transport of low-molecular-weight hydrophobic solutes (MW < 400 Da). The second mode included solute motion due to lateral diffusion of lipid molecules and is particularly important for high-molecular-weight solutes (MW > 400 Da) that partition preferentially in lipid bilayers but possess low diffusion coefficients due to their large size. The third mode included solute diffusion through pores, whilst the fourth mode included solute diffusion through shunt pathways. The last two pathways are shown to be important for hydrophilic solutes.

Mathematically, skin permeability to a solute (hydrophilic or hydrophobic) can be described by the following Equation 1.36:

$$K_p\,(cmh^{-1}) = K_p^{fv} + K_p^{lateral} + K_p^{pore} + K_p^{shunt} \qquad \text{(Equation 1.36)}$$

where K_p^{fv} corresponds to permeability associated with free-volume type of diffusion through lipid bilayers, $K_p^{lateral}$ corresponds to permeability of hydrophobic solutes due to lateral diffusion of lipids, K_p^{pore} corresponds to solute permeability through pores and K_p^{shunt} corresponds to solute permeability through shunts (hair follicles and sweat ducts). It is assumed that all four pathways are available to solutes for transdermal penetration.

Patel et al. (2002a) found MW to be a better predictive parameter among all the others employed in the equation; it also has the advantage that it is an easier descriptor to obtain and apply. However, it must be recognised that the dataset examined by those latter workers is dominated by hydrocarbons with relatively constant values in the ratio of molecular volume to MW. Fitzpatrick et al. (2004) reanalysed the same dataset as that of Patel et al. (2002a) and discussed the variability in the database.

1.8.3. Statistical Analysis

In statistics, regression analysis can be applied to any model when the focus is on the relationship between a dependent variable and one or more independent variables. For the majority of the QSPRs, as shown in Sections 1.8.2.1 to 1.8.2.3, simple regression analysis is the statistical method of choice, being simple, transparent and highly portable (Cronin & Schultz 2001). More specifically, regression analysis helps understanding how the typical value of the dependent variable changes when any one of the independent variables is varied, while the other independent variables are held fixed. Regression analysis is widely used

for prediction and forecasting, where its use has substantial overlap with the field of machine learning (Freedman 2005). Regression analysis is also used to understand which among the independent variables are related to the dependent variable and to explore the forms of these relationships. For assessing regression performance, the most common measurements that have been applied to the models described before (Section 1.8.2) consist of the regression coefficient (R^2), standard error (S) and Fisher's statistics (F). All these statistical parameters are associated with 'the goodness of fit' of a regression-based QSPR. The degree of freedom (N) is also reported in each case. Fisher's statistics is an indication of the fit of a regression equation to the training set data and can be defined as the ratio of the mean square to the residual mean square. It also provides statistical predictive capabilities, i.e. indicates whether regression coefficient is sufficiently large, considering the number of variables used. It ranges from zero to arbitrarily large numbers. Furthermore, it is important to have a measure of the error of prediction for a QSPR. The standard error of the estimate is the measure given for the majority of QSPR correlations, although other error statistics, such as standard deviation (SD) or mean absolute error, are occasionaly used instead. A good QSPR should have a prediction error close to the measurement error; that is, the QSPR is modelling the data as well as possible (Dearden et al. 2009).

Nevetheless, there are a number of disadvantages to using this method. Firstly, it is a linear technique and secondly, it is adversely affected by colinearity between independent variables (e.g. log P_{ow} and MW). It is not very clear whether regression analysis is a suitable tool for the development of QSPRs (Sun et al. 2008); nor is it clear whether linearity is appropriate for modelling of highly hydrophilic and hydrophobic molecules. Consequently, more recent methods such as Neural Networks (NN) (Section 1.8.2.4.2), Fuzzy Logic (Section 1.8.2.4.4) and others, for example Gaussian Process (GP, a stochastic process whose realisation consists of random values associated with every point in a range of times in order to obtain a normal distribution of data), are being upgraded to improve their performance in QSPRs studies. These new and upgraded methods and algorithms will be described in detail later and their advantages and disadvantages will be discussed thoroughly, in order to demonstrate their application potential in QSPRs studies (Peixun & Wei 2009).

1.8.4. Quality of the Datasets

Over the decades, a large number of data has been generated on the percutaneous penetration of a wide range of chemicals, including pesticides, cosmetics and pharmaceuticals. Studies have included work on human volunteers and *in vivo* studies using animal rodent, pig, guinea pig and, more recently, synthetic skin. There are numerous factors that can influence dermal penetration values, such as species variation, application site, dosing regimen, occlusion, sex and age, as well as interlaboratory and intralaboratory variations. While many of these studies on percutaneous penetration are unpublished (being company or governmental property), there are a number of studies in the open literature. There have been many different compilations of data (e.g. Flynn 1985; Johnson et al. 1995; Wilschut et al. 1995; Patel et al. 2002a; Vecchia & Bunge 2003a; USEPA 2004).

1.8.4.1. Datasets from Homologous or Closely Related Molecules

Apart from studies on single compounds, several investigators determined permeability data from homologous compounds or other series (Marzulli et al. 1965; Scheuplein & Blank 1971; Idson 1975; Roberts et al. 1977a; Wester et al. 1985; Idson & Behl 1987; Ridout & Guy 1988; Ridout et al. 1992).

1.8.4.2. Flynn Dataset and Expanded Datasets

The publication of the Flynn dataset was a milestone in the development of percutaneous absorption prediction. It comprised of 97 permeability coefficients for 94 compounds *in vitro* through human skin and for toluene, ethyl benzene and styrene *in vivo* in humans (Flynn 1990) and was for over a decade the largest dataset of skin permeability values. However, the Flynn dataset is a compilation of 15 different literature sources, with the inherent disadvantage of having a high degree of variability due to inter- and intralaboratory error as well as variation due to the skin being from different sources and locations on the body (Moss et al. 2002). Based on this dataset, Flynn and several others have proposed a number of algorithms to predict skin permeability. For further modelling studies, a number of datasets were compiled from various earlier publications. For example, in the study by Wilschut et al. (1995), data were given on 123 measured permeability coefficients of 99 different chemicals. Also, Patel et al. (2002a) collected a comprehensive dataset containing 186 permeability coefficients for 158 structurally diverse compounds. Furthermore, Vecchia & Bunge (2003a) presented a sizeable and diverse dataset of 170 measurements for 127 compounds covering relative MW from 18 to 584 Da and log P_{ow} values from -3.1 to 4.6. Finally, the EDETOX database is available, which is composed of data compiled from the published literature, produced from *in vitro* and *in vivo* percutaneous penetration studies. The data have been filtered in a variety of ways and extracted in printed reports or exported to MS Excel® spreadsheets. All available studies on a particular chemical were entered into the database and an assessment made as to whether information fit EDETOX criteria, according to which specific parameters such as concentration, area, vehicle, receptor fluid etc., were assessed and reported. The purpose of the database was to bring together *in vivo* and *in vitro* percutaneous absorption and distribution data.

1.8.5. The Need to Develop a New, more Predictive Model

The use of QSPRs in the prediction of skin permeability is important for transdermal drug delivery, in the cosmetic industry and for risk assessment of dermal exposure to toxic substances. The accuracy of the QSPRs discussed in Section 1.8.2 is indicated through their regression coefficient values, widely known as indicators of predictivity. Clearly, the closer the regression coefficient is to unity, the better the prediction may be taken as being. However, even though some regression coefficient values were shown to be quite high (El Tayer et al. 1991, $R^2 = 0.901$; Lien & Gao 1995, $R^2 = 0.96$; Potts & Guy 1995, $R^2 = 0.94$; Abraham et al. 1995, $R^2 = 0.978$; Pugh et al. 1996, $R^2 = 0.91$), the models need to be improved in terms of the data upon which they were originally developed (this is further discussed in Sections 2.11 and 2.12). The differences in protocols used for measurement of percutaneous penetration resulted in a collection of values that are not wholly consistent and this introduces a degree of variability in the resulting models. Moreover, to avoid the

limitations of linearity in the models as well as the inclusion of limited number of physicochemical inputs, new, more descriptive models must be developed, based on controlled data.

1.9. AIMS AND OBJECTIVES

1.9.1. Aims

In order to overcome the basic limitations of the existing QSPRs, the linearity problem and the data inconsistency, non-linear modelling based upon well constructed datasets might provide a more accurate prediction of percutaneous absorption for molecules with a wide range of log P values. Also, the inclusion of more input parameters might be expected to provide a more descriptive picture of the permeation process. The validation of the best selected model would then be performed by applying to the model new data, developed under controlled experimental conditions.

1.9.2. Objectives

The first objective of this study was to construct a novel consolidated dataset comprised of smaller datasets, by classifying all data available in the literature according to the corresponding experimental conditions employed. The second objective was to evaluate the existing QSPRs by using these newly constructed subgroups. A third step was to manually manipulate the data in the new subgroups by using linear statistical regression methods. However, the major objective of the thesis was the development of an improved non-linear model by using the best-selected data, i.e. those derived from experimental conditions close to real time conditions, by evaluating existing QSPRs, by performing variability classification of data available in the literature according to the corresponding experimental conditions employed and then by analysing each subgroup. The ultimate goal of the project was to validate the best-selected model by applying to it new data, experimentally developed under controlled conditions. In order to test the latter hypothesis (the validity of the best existing model) a small number of drug candidates were selected according to specific criteria (Chapter 5) i.e. availability, pricing, lipophilicity, theoretical predictions and degree of solubility in selected solvents, with the aims of determining the corresponding fluxes and permeability coefficients of the compounds under carefully-controlled conditions and of correlating these with those predicted by the available models.

Chapter Two

Variability in Skin Permeability Coefficient Measurements: Classification of Data According to the Experimental Conditions Employed

2.1. BACKGROUND AND RATIONALE

As already discussed in Section 1.8.4.2, the data upon which many QSPRs have been developed were predominantly obtained from one source, Flynn (1990). However, Flynn's dataset was shown to have the inherent disadvantage of a high degree of variability due to inter- and intralaboratory errors as well as a variation due to skin from different sources and location in the body (Moss et al. 2002). Furthermore, as a result of data repetition, more than one K_p value has been reported for a number of specific compounds and entered into the database, thereby contributing to the overall data variation.

Since the publication of the Flynn dataset, there have been a number of efforts to extend and expand it in terms of the number of chemicals and the coverage of the compounds. Such efforts have also assessed the data quality and, in most cases, variability in the data has been demonstrated. A number of compounds were found to be outliers: these included naproxen, atropine and nicotine, due to anomalous results (Degim et al. 1998). Repositories of data were also kept by the industry and regulatory bodies e.g. pesticide datasets with almost 300 dermal absorption studies of more than 160 different pesticides (Reddy & Bunge 2002; Jones et al. 2004). All these data have been generated in connection with research on the percutaneous penetration of a wide range of chemicals, pesticides, cosmetics and pharmaceuticals. For this reason, as a first step in the thesis a novel consolidated database (including smaller datasets and subgroups) was constructed by classifying all data available in the literature according to the corresponding experimental conditions employed.

2.1.1. Data Availability and Quality

For the development of QSPR models, a key feature is that all data must be consistent and reliable. In other words, in order to develop predictive models for skin permeation, all data should be measured using the same protocol, with skin from the same animal and measured ideally in one laboratory. Specifically, there are several ways of determining skin permeability values in water, as undissociated species, at a given pH and at a given ionic strength. There are also a number of different methods for the determination of skin permeability, each of which could conceivably yield slightly different results. Variations brought into the dataset by the use of measurements from different laboratories using different skin and protocols will lead to an increase in experimental error and result in a decrease in the statistical validity of the model. It is well known that the value of the permeability coefficient obtained from *in vitro* experiments can be strongly dependent on experimental techniques and conditions (Bronaugh 1989). As a consequence, it would be of great interest to obtain the largest possible, chemically heterogeneous database of skin permeability values, all measured in the same manner, within a realistic scheme.

It is true to say that a QSPR developer will never admit to having sufficient high quality data to model. Current models have been limited because of the quality of the data that were available. This problem of data quality has been partially rectified by more recent work (Vecchia & Bunge 2003a; Vecchia & Bunge 2003b) as well as data reported by the web-based EDETOX project. Although the current numbers of chemicals for which reliable skin permeability coefficients are available is relatively large (i.e. > 100), this

is still small in comparison with the total number of compounds that may enter the environment or to which a human may be exposed. This may limit the applicability of a model, particularly in terms of its lack of chemical heterogeneity. A representative selection of compounds that satisfactorily spans the chemical domain must be included in the dataset under construction (Schultz et al. 2003). Data for compounds from different chemical classes are often incorporated into QSPR correlations. This is acceptable on the proviso that the mechanism of action of all of the compounds is the same. It is fair to say that the accuracy of prediction is usually less for such correlations, partly because the data are drawn mostly from the published literature and hence have been determined in different laboratories. Of course, data for compounds within a single chemical class could also have been determined in more than one laboratory (Dearden et al. 2009).

To predict any quantity successfully, high quality data and an appreciation of the key factors that control the phenomenon are required. Regarding QSPR activity data, a number of workers have made suggestions concerning what constitutes 'high quality' (Cronin 2005; Cronin & Schultz 2003). Ideally, data would be obtained from the same laboratory, using a well defined and consistent protocol. For example, using the protocol published by the Organisation for Economic Cooperation and Development [OECD] for the testing of chemicals to quantify dermal absorption values using *in vivo* or *in vitro* techniques (OECD 2004a; OECD 2004b), or the protocol described by the International Organisation for Standardisation guideline (WHO 2006). Furthermore, the work should be performed according to Good Laboratory Practice (GLP) standards or the equivalent thereof. It must also be appreciated that as datasets become compilations of literature values, the quality of the final set is almost always reduced.

The intrinsic ability of compounds to permeate the skin can be estimated by the determination of the permeability coefficient. However, it is well known that the value of the permeability coefficient obtained by *in vitro* experiments can be strongly dependent on experimental techniques and conditions (Bronaugh et al. 1989). For this purpose, steady state diffusion should be established in *in vitro* experiments (Potts & Guy 1994) and then a number of factors need to be considered. Two of the most important factors are that the donor vehicle should keep the membrane exposed to a constant concentration of the permeant and that the receptor phase should maintain sink clearance conditions for the diffusing compound. Furthermore, the level of drug saturation in the vehicle must be defined. Depending on the saturated solubility of the drug in each vehicle, large differences in skin penetration can occur between vehicles that contain the compound at a fixed concentration. Vehicles in which the drug is at or near saturation will show an enhanced drug penetration rate, compared with those in which the drug is subsaturated (Walters & Roberts 2002). All measurements must be examined even more carefully when compounds with limited water solubility are included in the experiments, due to the more aqueous epidermal layer, in comparison to the stratum corneum. When penetration data were obtained carefully, taking into account the control of appropriate variables, good agreement between *in vivo* and *in vitro* measurements has been claimed (Bronaugh et al. 1989).

2.1.2. Intra- and Interlaboratory Variation in *in Vitro* Percutaneous Absorption Methodology

The presence of international guidelines has led to a partial standardisation of *in vitro* skin absorption studies for regulatory purposes. In the OECD guidance document (OECD 2000b), the design of *in vitro* skin absorption studies is defined, with both static and flow-through diffusion cell types being considered suitable. In order to prevent underestimation of skin absorption, the test compound should be soluble in the receptor fluid, but the receptor fluid should not alter the barrier properties of the skin membrane. Skin membranes can be prepared in various ways, but the use of skin membranes with a thickness of more than 1.0 mm (epidermis and dermis) is not recommended and must be justified by the researcher, since the absorption of lipophilic compounds might be impeded by a thick dermis. This guidance has been proved useful for both investigators in the laboratory and for regulatory agencies, which evaluate this type of data for risk assessment purposes.

Only very limited data exist for the intra- and interlaboratory variation of *in vitro* skin absorption studies. A good correlation of *in vitro* absorption has been reported through full thickness pig skin in two laboratories (Pappaterra Mendoza et al. 2000). The intra- and interlaboratory variation of methyl paraben (MP) absorption has been assessed in 18 laboratories using an artificial (silicone rubber) membrane (Chilcott et al. 2005). Standardised calculations of MP flux were determined from the data submitted by each laboratory by applying a predefined mathematical model and the coefficient of variation between laboratories was found to be approximately 35%. There was a four-fold difference between the lowest and highest average flux values and a six-fold difference between the lowest and highest individual flux values. Intralaboratory variation was lower averaging 10% for five individuals using the same equipment within a single laboratory. In another study, the *in vitro* absorption of benzoic acid, caffeine and testosterone (compounds having a range of different physicochemical properties) through human skin (9 laboratories) and rat skin (1 laboratory) was determined (Van de Sandt et al. 2004).

All laboratories performed their studies according to detailed and defined protocols (dose, exposure time, vehicle, receptor fluid, preparation of membranes, analysis) and each laboratory performed at least three independent experiments for each test chemical. The ranking of dermal penetration of all chemicals was the same for all participating laboratories. There was some variability between the results due to a large extent to interindividual variability in absorption between samples of human skin and skin from different sources. Finally, temperature variation in diffusion cells was identified as a potential factor contributing to interlaboratory variation of dermal absorption (Romonchuk & Bunge 2004).

2.1.3. Principle of the Standard *in Vitro* Tests Using Skin Samples

The test substance is applied to the surface of a skin sample separating the two chambers of a diffusion cell. Skin obtained from a number of mammalian species, including humans, can be used. The chemical remains on the skin for a set time under specified conditions, before removal by an appropriate cleansing procedure. The receptor fluid is sampled at time points throughout the experiment and analysed for the test chemical and / or metabolites.

2.1.3.1. Test Chambers

There are two basic designs of test chambers, the one-chambered diffusion cell – the static cell (Franz 1975) and the flow-through cell (Bronaugh & Stewart 1985). *In vitro* protocols generally describe the use of either type of cell but it is the Franz diffusion cell (Figure 1.8) which is one of the most widely used (Friend 1992). Such a diffusion cell is relatively simple in design; the receptor fluid beneath the skin is manually sampled by removing aliquots periodically for analysis (Bronaugh 2004b) and it can run as a static or a stirred cell. Flow-through cells are characterised by continuously replacing the receptor fluid, which represent more or less *in vivo* conditions. Such a cell is simple in design, costs relatively little and can be produced with a wide range of openings to accommodate different surface areas of skin (Bronaugh 2004b). In contrast to the static cell types, flow-through cells provide the continuous replacement of a nutrient medium necessary to maintain physiological conditions and are recommended for metabolism studies (Bronaugh et al. 1999; Bronaugh 2004b).

2.1.3.2. Finite / Infinite Dosing

Finite dose is a close representation of the 'in use' approach. Infinite dose conditions can be assumed if the concentration of the agent in the donor compartment is constant throughout the experiment and if the receiver compartment is an effective sink for the agent (Kemppainen & Reifenrath 1990). This latter condition can be maintained with receptor concentration being less than 10% of the donor concentration during the experiment. Under such conditions, a constant driving force and gradient will be established after an equilibrium period and the rate of the appearance of agent in the receptor compartment will be constant. In the infinite dose procedure the dose solution is applied in excess and is occluded for the duration of the study (Sartorelli et al. 2000; OECD 2004c). In the finite dose regime, the dose solution or formulation is applied in a volume sufficient to cover the skin and the donor chamber normally remains unoccluded. In finite dose situations, the loss of the agent from the donor compartment results in a significant decrease in the concentration between the donor and the receiver compartments during the experiment.

2.1.3.3. Choice of Skin

The choice of skin depends on the purpose of the test and the availability of skin samples. Skin from human and animal sources can be used but the use of human skin is subject to respective national and international ethical considerations and conditions (ECETOC 1993). Cnubben et al. (2002) studied the *in vitro* skin penetration of [^{14}C] ortho-phenylphenol (log P_{ow}= 3.28) through human and rat viable skin, human and rat epidermal membranes and perfused pig ears (four to six skin membranes were used per experimental group). Typical human *in vitro* experiments could involve the use of female abdominal and / or breast skin obtained (with consent) at autopsy or from cosmetic surgery. Skin samples that may be used are split-thickness (200-400 / 500 µm) or full-thickness (500-1000 µm) skin preparations (OECD 2004c; USEPA 2004), although full-thickness skin is not recommended for use for absorption studies in general (Bronaugh et al. 1986). The skin might be shaved and the subcutaneous fat removed. The influence of the

skin thickness (0.5-1.3 mm) on percutaneous penetration has been studied using caffeine, testosterone, butoxyethanol and propoxur (Wilkinson 2004). Some changes in the maximum flux and the cumulative amount in the receptor fluid, dependent on the skin thickness, were seen, but no clear effects on the extent and rate of the penetration was observed, as the relationship between skin thickness and physicochemical properties is complex (Wilkinson 2004). Full-thickness and split-thickness skin is often trimmed with a dermatome in order to obtain skin samples of uniform shape and thickness (Steiling et al. 2001). Furthermore, the skin samples should be prepared to fit the size of the experimental cell. *In vitro* penetration in rat, human and pig skin expressed as cumulative amount reaching the receptor fluid can be seen in Figure 2.1.

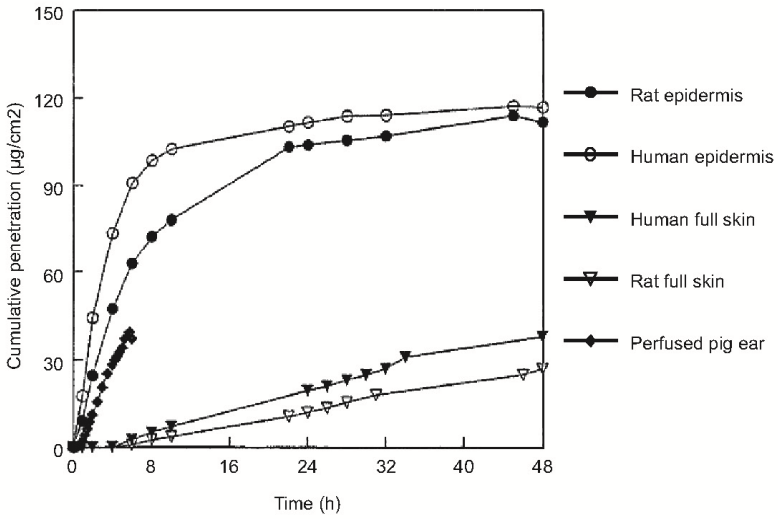


Figure 2.1. *In vitro* skin penetration of ortho-phenylphenol in rat, human and pig skin expressed as cumulative amount reaching the receptor fluid (Cnubben et al. 2002).

2.1.3.4. Analytical Method

Previously, for practical reasons, the test substance employed in skin diffusion studies would have been routinely radio-labelled (preferably using ^{14}C tagging at a metabolically stable position). However, more recently, the use of radio-labelled compounds has become less popular due to the fact that synthesis is a costly process and moreover, as analytical techniques have improved in sensitivity, an appropriate validated assay procedure is now commonly employed. This usually involves the use of other analytical techniques, such as those introducing HPLC with either UV or MS detection.

2.1.3.5. Vehicle

The choice of the vehicle may have an influence on the skin permeability results. The vehicle effect is described by the vehicle / stratum corneum partition coefficient (K_m), which is an important factor in

determining the rate of penetration of a chemical (Scheuplein & Blank 1971). This coefficient describes the relative affinity of a chemical between the vehicle in which it is applied and the stratum corneum (Suskind 1977). The more soluble the penetrant in the vehicle, the more likely it is to be retained within the vehicle. A greater solubility in the stratum corneum than in the vehicle promotes penetration (Van der Valk et al. 1985) into the stratum corneum. But if the drug is too lipophilic, then it might remain in the stratum corneum and not diffuse further. Solutes, which are held firmly in the vehicles, exhibit low activity coefficients (low escaping tendencies) and, thus, low rates of penetration. The thermodynamic activity of the drug is obviously, as already discussed in Section 1.5.1, the ultimate determinant of biological activity (Florence & Atwood 2006).

2.1.3.6. Anatomical Site

The percutaneous absorption of acetylsalicylic acid, benzoic acid, caffeine and benzoic acid sodium salt (radio-labelled) was measured in humans on four body sites (arm, abdomen, post auricular and forehead), using a tape-stripping method. The stratum corneum of the treated area was removed by 15 successive strippings and the radioactivity present in the horny layer measured. Relative skin permeability was as follows: arm ≤ abdomen ≤ post auricular ≤ forehead. It is noteworthy that whatever the compound applied, the forehead is about twice as permeable as the arm or the abdomen (Rougier et al. 1987; Rougier et al. 1999). Figure 2.2 demonstrates that the absorption of hydrocortisone was also shown to be dependent upon the anatomical site (Wester & Maibach 1999). Even though anatomical variation does reflect everyday use, standardisation must be considered in model development, if that model is to be used for predictive purposes in formulation development.

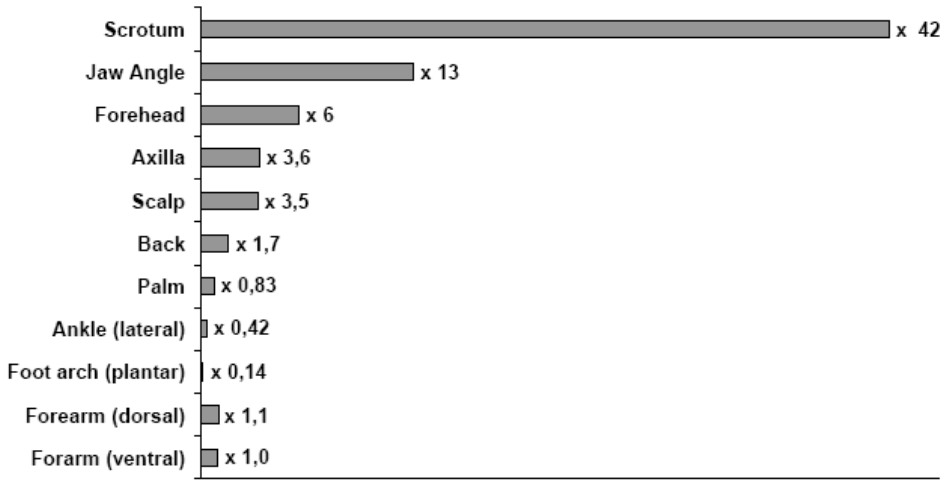


Figure 2.2. The effect of anatomic region on the permeation of hydrocortisone (adapted from Feldman & Maibach 1967, in Wester & Maibach 1999).

2.1.3.7. Composition of Receptor Fluid

The receptor fluid should not act as barrier to absorption (due to poor solubility of the test compound) and not affect skin preparation integrity (OECD 2004a). The prime objective of a receptor fluid is to provide sink conditions for the penetrating molecule so that the transfer of the penetrant from the skin into the receptor does not influence the rate of release. It is generally accepted that sink conditions exist provided that the concentration of penetrant in the receptor phase does not exceed 10% of its saturated solubility (Jones et al. 1989). *In vitro* percutaneous absorption experiments are usually performed using aqueous-based solutions as the receiver phase. However, for poorly-water-soluble lipophilic compounds, water may cause flux-limiting solubility or unstirred layer phenomena. These will have the effect of obscuring the true flux of the drug through the skin. *In vitro* human epidermal permeability coefficients of a series of aliphatic alcohols (C1-C10, log P between 0.72 and 4.06) using two different receptor solutions [water and 4% Bovine Serum Albumin (BSA) in phosphate-buffered saline] were determined (Cross et al. 2003) and it was concluded that BSA containing receptor phase allowed a better estimation of real permeability parameters for lipophilic compounds due to its increased solubilising capacity. Still, isotonic saline is probably the most popular receptor fluid (Bronaugh et al. 1985; Skelly et al. 1987; Jones et al. 1989).

2.1.3.8. Duration of Exposure and Sampling Time

The exposure time may vary between a few minutes for a 'rinse-off' product, 8 h for exposure to industrial products and 24 h for longer 'leave-on' products. It is important to sample the receptor fluid for at least a 24 h period and up to 72 h. The duration of the experiment depends on the absorption profile of the compound under investigation. For the majority of compounds, the profile is determined within the first 24 h period but caution has to be taken if the sample is exposed more than 72 h, due to the possibility of the deterioration in the structural integrity of the skin membrane.

2.1.3.9. Temperature and Ionisation Effect

Importantly, for the new database construction the effects of temperature (i.e. the receptor phase generally maintained at 37°C) and of ionisation should also be considered. Both these factors are important and until now have been overlooked in some cases when skin permeability coefficients have been obtained. The effect of temperature on the skin permeation of terodiline hydrochloride and the free base form was examined. The *in vitro* penetration experiment at 25-50°C was carried out using the full-thickness skin and the stratum corneum sheet of Wistar rat. The relationship between the flux and the phase state of the stratum corneum lipids was evaluated based on the data obtained. It was shown that increasing temperatures resulted in increased penetration of both hydrochloride and free base forms (Taro et al. 1998). Heat is known to increase skin permeation of drugs by several mechanisms. Higher temperatures increase microcirculation and blood vessel permeability, which facilitates drug transfer into the systemic circulation. A rise in temperature may also increase drug solubility both in the patch formulation and within the skin, thus, increasing the release rate of

the drug from local skin tissue into the systemic circulation. Since heat increases skin permeation, there are concerns that excessive exposure to heat will increase absorption of transdermally delivered drugs and lead to overdosage. In fact, the U.S. prescribing information for Duragesic warns patients to avoid exposing the application site to direct external heat sources (Bogner & Wilkosz 2003). Abraham and Martins (2004) reported that correcting for temperature and accounting for ionisation greatly improved the statistical fit of the model and its predictive capability. In one *in vitro* study, saturated suspensions of the model penetrants, MP, Butyl Paraben (BP) and Caffeine (CF) in deionised water (vehicle) were applied at maximal thermodynamic activity to membranes contained in Franz cells (Akomeah et al. 2003). Experiments were performed at temperatures ranging from 23 °C to 45 °C using the infinite dose method. The penetrant diffusivity (diffusion coefficient) in the vehicle was shown to be totally dependent on temperature and not on changes in donor solubility. In addition, epidermal flux and retention of all penetrants in the epidermis was shown to be affected by temperature. The amount of penetrant retained was found to be in the order BP > CF > MP whilst the transdermal fluxes increased in the order MP > BP > CF with increasing receptor temperature. Another point that must be considered when initiating the development of a new QSPR is the use of compounds that are not ionised (Akomeah et al. 2003). Whilst ions permeate the skin at a reduced rate (compared to the neutral molecule), ionised compounds have greater solubility in the receptor phase and this tends to increase permeation (Jones et al. 2004). Such opposing effects can lead to apparent inconsistencies in the data. However, most of the data available in the literature do not determine / report the pH of the environment under which these experiments were conducted; consequently it is difficult to determine / record the actual state of ionisation of the compounds under investigation. Even if the pH is determined, more work is required to elucidate the effect of ionisation on skin permeability.

2.1.4. Recommendations for *in Silico* Model Development

When modellers are developing algorithms, the differences in protocols used for measurement of percutaneous penetration, which can induce a high degree of variability, should be considered carefully. Only those data deemed to be high quality should be used for modelling. Ideally, some assessment of the chemical space of the currently available data should be made and this highlights an area where there appears to be a deficiency of knowledge. Although a number of skin permeability measurements can be used, usually skin permeability coefficients are the preferred consistent parameter employed. For successful modelling and to ensure high-quality data, the data must be standardised. In addition, it has been shown that modellers should always consider (when developing a new QSPR) effecting an adjustment for temperature and correcting for ionisation. Skin permeability data for QSPR modelling should be treated as passive diffusion data and modelled in an empirical manner. Ideally, this means that QSPR development should commence with descriptors that reflect the process modelled. Thus, descriptors for partitioning (i.e. log P) and molecular size (e.g. MW or similar) are recommended. The relevance of properties such as hydrogen bonding in QSPR for skin permeability has been emphasised. Yet, its exact role is uncertain and, so far, its true relevance remains undetermined, therefore it should be treated with caution as a parameter in model development. All QSPR

development should consider and abide by the guidance on good practice in modelling (Livingstone & Cronin 2004). As already discussed in Section 1.8.3, of the statistical techniques available, regression analysis is the most simplistic and has a number of other advantages over the alternatives, such as high portability, ease of use and interpretation.

2.1.5. Chemicals to be Selected for Testing

When selecting chemicals for developing QSPRs, acceptance criteria must be applied to each set of data employed. There are many recommendations made by various bodies in the United States of America [USEPA (U.S. Environmental Protection Agency) 2004, FDA Scale-Up and Post Approval Changes (SUPAC-SS) and the International Pharmaceutical Federation in collaboration with the American Association of Pharmaceutical Sciences (FIP / AAPS)] and in Europe (European Commission Guidelines 2004) further to guidelines referred to OECD (Organization for Economic Co-ordination and Development) 2004 a-d. In addition to these, other recommendations made to CEFIC (*Conseil Européen des Fédérations de l'Industrie Chimique* - European Chemical Industry Council) by the meeting members for the selection of chemicals for developing the acceptance of QSPRs as a valid and reliable method of predicting the permeability for chemicals, are summarised below:

1. The chemicals must be readily available and produced in high volume in industry;
2. The chemicals must be chosen in conjunction with industry;
3. The log $P_{o\text{-}w}$ values must vary from -3 to 7 and MW from 30 to 1000 Da (an elliptical space on a two dimensional plot of chemicals by these two parameters).

The recommendations / guidelines generated by the above authorities were to be extended in this work such that specific, narrower in nature, acceptance criteria were set (and these are fully described in the method section below). A large number of QSPRs have been developed for the prediction of skin permeability and they were available in the literature prior to the construction of a consolidated database. However, the limited applicability, in terms of accurate prediction, of many of the QSPRs developed is a matter of concern. This was particularly evident in cases where large discrepancies were observed between permeability coefficient values for the same compound with more than one measured value (Jones et al. 2004).

2.2. AIM AND OBJECTIVES

2.2.1. Aim

The aim of this phase of work was to seek to assess the quality of the current data available which might be used in current model appraisal and future model development. In addition, the range of parameters available to assess the absorption of dermally applied compounds would be collected into datasets. It is highly likely that, as with previously developed models, skin permeability coefficients are the best parameter to employ,

although, in future model development, the database should comprise of high quality data obtained under standardised conditions. In addition, all data should ideally be corrected for ionisation. Skin permeability is a passive diffusion process and all QSPR developments should include descriptors that reflect the modelled process.

2.2.2. Objectives

The objective of this chapter is to conduct a detailed analysis of the available *in vitro* dermal absorption data with a view to classifying them according to the corresponding experimental conditions employed. Such developed databases would then be employed to retest the validity of current models as well as to develop reliable novel predictive models (see Chapters 3 and 4 respectively).

2.3. METHOD

All the data available in the literature were initially separated into three distinct databases, Database A, Database B and Database C, according to specific criteria described in Sections 2.3.1, 2.3.2 and 2.3.3 respectively. Each database was further divided into datasets according to the nature of the data included in the database. Finally, the human, mouse and rat datasets of Database C were in their turn split into corresponding groups (Groups A1-A24 for the human skin dataset, Groups B1-B7 for the rat skin dataset and Groups C1-C6 for the mouse skin dataset). The chart in Figure 2.3 illustrates this database - dataset - group arrangement.

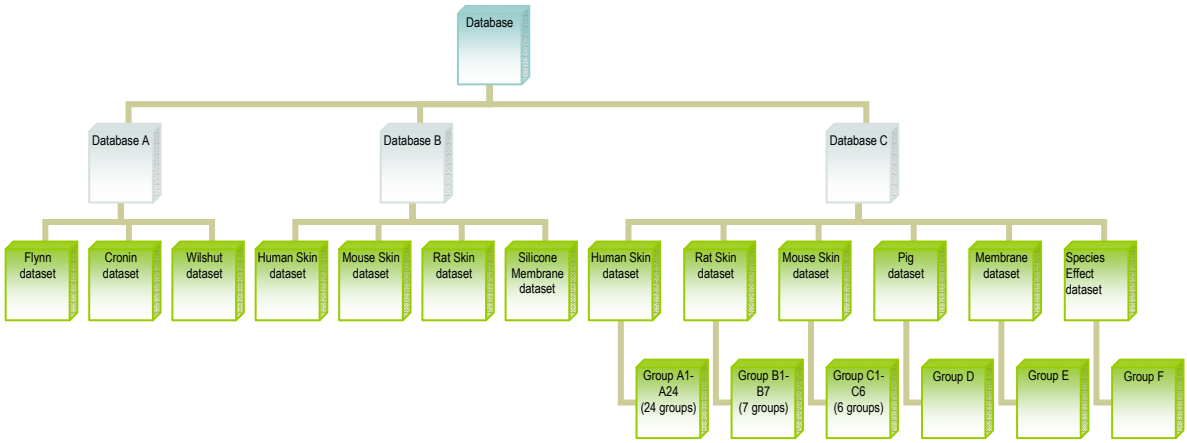


Figure 2.3. Classification of data.

2.3.1. Data Available in the Literature – Database A

As already discussed in Sections 1.8.2.2 and 1.8.4.2, the most frequently cited datasets based on human skin data are the Flynn dataset, the Wilshut dataset and the Cronin et al. (1999) dataset (which combines various other data with the Flynn dataset). For the purpose of this thesis these three datasets are collectively termed 'Database A' (Appendix 1). Therefore, Database A is a reference database, consisting of the most popular

datasets available in literature upon which the majority of current QSPRs have been developed. As will be discussed in detail in Chapter 3, most of the data in these datasets have been derived from a variety of sources and, when experimentally determined, most of these data were generated without a standard, or even a specific experimental framework. As a matter of consistency, for all the datasets available in Database A, all log P values were recalculated using the KOWWIN programme, developed by the EPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC 2011). Even though a large number of methods has been developed for log P estimation, EPI Suite's KOWWIN program has the advantage that its calculations are based on the relatively minor structural differences between the target and the analogue, which introduces less uncertainty than constructing the actual molecule from basic fragments. This approach is potentially more accurate for log P estimations and has been incorporated into the OECD QSAR application toolbox (Cronin 2010).

2.3.2. Initial Reorganisation of the Data – Database B

All data were grouped together according to the membranes employed during the permeability experiments. A large database of 167 compounds was initially developed, comprising of 70 compounds in the human skin dataset, 43 compounds in the mouse skin dataset, 36 compounds in the rat skin dataset and, finally, 18 compounds in the silicone membrane dataset. Experimental data were taken from published studies on *in vitro* dermal drug penetration conducted on the range of membranes. However, before conducting a search, the type of data required had to be identified. Several review articles and other experimental work were utilised in assembling the database. These included a section of the Flynn (1990) dataset (Table 2.2) and the Ghafourian & Fooladi (2001) datasets as well as data published by Degim et al. (1998), Modamio et al. (2000), Hadgraft et al. (2000b), Fang et al. (2003) and Suhonen et al. (2003). More published data used for the construction of Database B are listed in Table 2.1. All datasets that resulted from the construction of Database B are summarised in Appendix 2.

Table 2.1. Published data used for the construction of Database B.

Skin Type	References
Human	Ritschel et al. (1989); Roy & Flynn (1989); Flynn (1990); Johnson et al. (1997); Degim et al. (1998); Hadgraft et al. (2000b); Modamio et al. (2000); Ghafourian et al. (2001); Fang et al. (2003); Suhonen et al. (2003).
Mouse	Waranis & Sloan (1987); Diez et al. (1991); Ghosh et al. (1992); Jain et al. (1995); Arellano et al. (1996); Hashiguchi et al. (1997); Shaker (2003); Suhonen et al. (2003).
Rat	Diez et al. (1991); Hatanaka et al. (1992); Johnson et al. (1995); Borras-Blasco et al. (1997); Fuhrman et al. (1997); Fang et al. (2003); Suhonen et al. (2003)
Silicone	Hagen et al. (1987); Flynn (1990); Hatanaka et al. (1992); Geinoz et al. (2002).
Mouse	Roy & Flynn (1989); Shah et al. (1991); Knutson et al. (1993); Fuhrman et al. (1997); Liaw & Lin (2000); Ghafourian et al. (2001).

The objective of the search was to obtain molecular weight (MW), partition coefficient (log P), Hydrogen bond acceptor (Ha) and donor (Hd) activities, Fedors' solubility and permeability coefficient (K_p) for each compound. Similarly to section 2.3.1 (Database A), since there are numerous log P values assigned for a specific compound in the scientific literature, many of which have been derived using a number of experimental and computational methods, it was decided to recalculate all log P values using the KOWWIN program, developed by the EPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC 2011). Additionally, the MW, Ha and Hd values were calculated from the Cambridge Soft Chemoffice Ultra (Cambridge Soft Corporation, 2006) simply by inserting each compound's simplified molecular input line entry system (SMILES) number into the program. The SMILES program was developed in mid-1980s by Earl Zwicker and Ken Schug. Finally, Fedors' solubility was manually determined by calculating the internal energy as well as the molecular volume of a compound. Specifically, the Fedors' group substitution method is based on the determination of the solubility parameter of a compound (δ) by using the following Equation 2.1:

$$\delta = (\Delta u / \Delta V)\, 0.5 \qquad \text{(Equation 2.1)}$$

where Δu represents the substituent fragment constant and ΔV represents the fragmental molar volume constant (Fedors 1974).

2.3.3. Further Refinement of the Compound Databases – Database C

A larger dataset containing 310 compounds (600 K_p values) was developed by combining all data existing in the EDETOX database (edetox.ncl.ac.uk) with that published by Wilshut et al. (1995), Patel et al. (2002a) together with other *in vitro* data derived by other separate sources. These sources included the Merck Index 14th edition (obtainable from www.medicinescomplete.com), British Pharmacopoeia (www.pharmacopoeia.co.uk), Martindale (obtainable from www.medicinescom plete.com), EPIWIN™ (www.epa.gov), ChemID plus database (chem.sis.nlm.nih.gov/chemidplus), EDETOX database as well as online journal databases such as Sciencedirect.com (www.sciencedirect.com), PubMed (www.pubmed.com), Web of Science (wos.mimas.ac.uk), Ingenta (www.ingenta.com/journals) and the Highwire (jpet. aspetjournals.org). Regarding the Flynn dataset, only those permeability coefficient values that had been derived under specific experimental conditions were included in the refined Database C. From the 94 compounds, only 37 compounds (Table 2.2) were included in the modified database (Database C). The compounds for which experimental conditions have been adequately defined are shown in Table 2.2 and the remaining 57 compounds from the Flynn dataset were excluded.

Table 2.2. The 37 compounds taken from the Flynn dataset.

No	Compounds	No	Compounds
1	2-cresol (o-cresol)	20	ethanol
2	2-ethoxyethanol	21	fentanyl
3	2-methoxyethanol	22	hydrocortisone
4	2-naphthol	23	hydromorphone
5	3-cresol (m-cresol)	24	ibuprofen
6	3-nitrophenol	25	meperidine
7	4-bromophenol	26	methanol
8	4-cresol (p-cresol)	27	morphine
9	aldosterone	28	n-nitrosodiethanolamine
10	aniline	29	n-octanol
11	β-estradiol	30	naproxene
12	benzoic acid	31	nicotine
13	chloroxylenol	32	phenol
14	codeine	33	pregnenolone
15	cortexolone	34	progesterone
16	corticosterone	35	resorcinol
17	cortisone	36	salicylic acid
18	estriol	37	testosterone
19	estrone		

Database C (shown in Appendix 3) comprised all compounds, for which the corresponding permeability coefficients were determined using specific experiments carried out with the use of defined, detailed protocols. A minimum set of criteria were required to describe all experimental skin diffusion protocols such as type of skin, vehicle, dose, loading, area of exposure, exposure time, receptor fluid, diffusion cell, method of membrane preparation, analysis, study length and temperature. These are described in more detail below. Database C, as discussed in Section 2.3.2, contained 310 chemicals with MW ranging from 18.02 Da (water) to 959.17 Da (decabromodiphenyl oxide), log P values ranging from -4.47 (glyphosate) up to 8.39 (DEHP) and with melting points ranging from -142 ºC (1-methoxylpropan-2-ol) to 1453 ºC (Nikel).

The difference between Database C and Database B, described in Section 2.3.1, is that Database C contains compounds with permeability coefficients that were derived under specific experimental conditions, which were all reported in the literature. Consequently, the permeability coefficients that were derived from experiments the conditions of which were not fully available in the literature were eliminated. These coefficients correspond to compounds which were included in Database B, such as aspirin, rafinose, sucrose, prednisolone pentodecanoate, nifedipine, undecanoate, hydrocortisone haxanoate etc., as shown in Appendix 3. Moreover, additional data from the EDETOX database and the literature up to 2008 were incorporated into Database C.

2.3.3.1. Data Entry

Databases A, B and C are incorporated in Appendices 1, 2 and 3 respectively. Each entry was triple-checked by the author in the following manner: first the literature was consulted and published data were entered onto

the MS Excel™ spreadsheets; then, the entries were confirmed by referring back to the original text; finally, a second person irrelevant to the research went over the numbers and units to corroborate all entries.

2.3.3.2. Type of Skin

As already discussed in Section 1.7.2, there are significant differences between the dermal absorption observed in laboratory animals and that in humans. For the majority of chemicals, laboratory animal skin is considerably more permeable (ECETOC 1993; Vecchia & Bunge 2005). Database C was first divided into five smaller datasets, having in common the skin membrane (human, rat, mouse pig skin or synthetic membrane) used for determining the permeability coefficient and maximal flux derivation. These datasets are detailed below (Datasets A to E). However, for certain compounds there were more than one K_p values reported in the literature, derived under different experimental conditions. Therefore, for some compounds included in the following datasets, more than one K_p value was included.

Dataset A: Human skin dataset comprised 145 compounds with 269 experimentally determined permeability coefficients.

Dataset B: Rat skin dataset comprised 77 compounds with 147 experimentally determined permeability coefficients.

Dataset C: Mouse skin dataset comprised 47 compounds with 114 experimentally determined permeability coefficients.

Dataset D: Pig skin dataset comprised 20 compounds with 35 experimentally determined permeability coefficients.

Dataset E: Other membranes: Synthetic membrane (silastic membranes) dataset and skin equivalent dataset (Graftskin™, Skinethic™, Testskin™) comprising 21 compounds with 39 experimentally determined permeability coefficients.

2.3.3.3. Effect of Lipophilicity and Molecular Weight

2.3.3.3.1. Lipophilicity (log P)

As discussed in Section 1.4.2, lipophilicity is regarded as an important factor in determining skin permeability. Consequently, all datasets (Human, Rat, Mouse, Pig, Membrane) were further split into the following categories (Appendix 4):

Human skin data:

- Subgroup 1: log P (-4.47) - (0.84) (38 compounds)
- Subgroup 2: log P 1.00 - 2.94 (62 compounds)
- Subgroup 3: log P 3.03 - 8.39 (44 compounds)

- Subgroup 4: no log P value reported (1 compound)

Rat skin data:

- Subgroup 1: log P (-3.01) - (0.84) (16 compounds)
- Subgroup 2: log P 1.03 - 2.99 (25 compounds)
- Subgroup 3: log P 3.03 - 8.39 (36 compounds)

Mouse skin data:

- Subgroup 1: log P (-4.27) - (0.84) (16 compounds)
- Subgroup 2: log P 1.51 - 2.82 (12 compounds)
- Subgroup 3: log P 3.02 - 8.10 (19 compounds)

Pig skin data:

- Subgroup 1: log P (-3.01) - (2.90) (12 compounds)
- Subgroup 2: log P 3.28 - 5.81 (8 compounds)

Membrane skin data:

- Subgroup 1: log P (0.16) - (2.90) (7 compounds)
- Subgroup 2: log P 3.02 - 6.79 (14 compounds)

2.3.3.4. Effect of Experimental Conditions Employed in K_p Determination

Many general models (as opposed to 'local' models developed in one laboratory) are constructed from data which have been compiled from different sources and which have been generated in different laboratories. Where there is more than one source of K_p value for the same compound substantial differences are observed. However, it has generally been accepted that the scale of variance observed is acceptable and within the range of variability expected in skin delivery experiments (Moss et al. 2002). Nevetheless, such variance is therefore translated into any models subsequently derived and this may be reflected in the statistical validity and accuracy of the model. By taking into consideration the variability existing between experiments, each dataset (human, mouse, rat, pig, membrane) of Database C was broken down into smaller subgroups (Groups) according to common experimental similarities, such as type of membrane, site, vehicle, cell type, study length, temperature, analytical method and receptor fluid. With regards to the construction of the new database, the studies entering the database had to meet specific criteria. All of the following parameters had to be clearly stated:

1. Type of membrane. Three types of skin membranes can be prepared for *in vitro* experiments: epidermal membranes (thickness of approximately 0.1 mm, prepared by heat separation, chemical or enzymatic separation), split-thickness skin (thickness of 0.2 - 0.5 mm prepared using a dermatome) and full-thickness skin (thickness of 0.5 - 1.0 mm).

Also, the stratum corneum (thickness of 0.01-0.02 mm) can be extracted from the full thickness skin, but such samples require careful handling in experimentation due to their extreme thinness.

2. Site: abdominal or breast skin was considered to be the most appropriate selection (Jones et al. 2004). Yet, at Database C skin data from other sites were also employed.
3. Chemical concentration (of chemical applied).
4. Dose Volume (volume of chemical applied to skin).
5. Area (area of skin to which the chemical was applied).
6. Vehicle (application medium): The most commonly used vehicles are neat compound (especially if the test compound is liquid at RT) or saturated solutions in water, propylene glycol, physiological buffer etc. Solvents are likely to affect the conformation of stratum corneum in a way that diffusion and partitioning could be modified. The majority of studies on skin permeation are based on the penetration of individual chemicals. Nonetheless, there are several attempts towards an investigation of the effect of incorporating more than one component within the chemical mixtures (Ghafourian et al. 2010b).
7. Cell type: Static or flow-through cells were both accepted.
8. Species (of animal used in the study).
9. Exposure time (i.e. the length of time the chemical was left on the skin): experiments were conducted over a 24 h period and were completed within 48 h.
10. Analytical method (i.e. the method by which the results were determined): for radiolabelled substances scintillation counting was usually performed whereas for non-radiolabelled substances HPLC or GC analysis was appropriate.
11. Receptor fluid (the medium that bathes the underside of the skin). For water-soluble compounds, the use of normal saline or an isotonic buffer saline solution was sufficient. Alternatively, a physiological buffer was needed to maintain viability of the skin for at least 24 h.
12. Temperature (temperature of the receptor fluid / skin / water bath during *in vitro* experiments): the rate and the extent of skin absorption was temperature-dependent, the skin surface temperature was maintained constant at 32 °C.

2.4. Results and Discussion: Analysis of the Datasets

2.4.1. Database A

Database A consists of the Flynn dataset, the Wilshut dataset and the Cronin et al. (1999) dataset (Appendix 1). Specifically, as already discussed in Sections 1.8.2.2 and 1.8.4.2, the Flynn dataset was assembled of 97 human skin K_p values for 93 compounds with MW ranging between 18.01 and 764.95 and log P value ranging between -4.27 and 5.49. It consists of measured permeations from aqueous solubilities and three *in vivo* measurements for styrene, ethylbenzene and toluene (Vecchia & Bunge 2003a). Most of the permeability coefficients were measured from loss of

chemicals in the vehicle before steady state was reached. Therefore, we cannot tell for most of the compounds if steady state was reached, especially for the largest molecules, such as digitoxin (Cronin 2006).

Regarding the Cronin et al. (1999) dataset, upon which the Cronin et al. (1999) model was developed (Section 1.8.2.3.1), the permeability coefficients for the passage of 114 compounds through human skin *in vitro* were taken from Kirchner et al. (1997) and were used as listed in units of cmh^{-1} (Appendix 1). However, seven outliers were removed from these data, resulting in 107 compounds with MW ranging between 30.03 and 390.56 and log P values between -1.71 and 5.39. The most significant of the seven outliers was propylene dichloride, which appeared as a gross outlier and an influential value. This may be a spurious permeability value as it was the only positive permeability coefficient in the dataset. Two of the outliers (estriol and hydrocortisone) were steroids. Other workers, e.g. Barratt (1995b) and Kirchner et al. (1997) identified steroids as outliers to QSPRS models for permeability. Barratt (1995b) omitted steroids entirely from subsequent models. Hydrocortisone, which was one of the steroids, was also considered as an outlier, since it was one of the six steroids found to have a lower permeability coefficient by Johnson et al. (1995). Unfortunately, there are no comparable data for estriol. Atropine and etorphine, although not steroids, have been excluded from the dataset due to their complex fused ring structures (Cronin et al. 1999). The remaining two outliers (digitoxin and sucrose) were atypical of this dataset as they were able to form many more hydrogen bonds (22 and 26, respectively) than the other compounds.

Furthermore, the Wilshut dataset, upon which the revised Robinson (1995) model (Section 1.8.2.2.8) and the revised Brown and Rossi (1995) model were developed, comprises 123 permeation coefficients and embodies a group of 99 different compounds applied to the skin in an aqueous solution. These chemicals represent a lot of chemical classes, for instance monuaromatic hydrocarbons (benzene), volatile halogenated hydrocarbons (1,1,1, trichloroethane), phenols (o-cresol) and steroids (prednisolone and progesterone). Molecular weight (MW) ranges from 18.01 to 764.99 g/mol. Water accounts for the lowest MW and digitoxin for the highest. The average molecular weight is 237.90 g/mol. The logarithm of the octanol-water partition coefficient (log K_{ow}) has an average of 1.75. Sucrose has the lowest and hydrocortisone methylsuccinate the highest log K_{ow}, respectively -4.27 and 5.58. These data are a compilation from both literature and regulatory sources (Flynn 1990; Wittiker et al. 1993). As these data come from a variety of sources, it may be assumed that there is variability in the exact methodology (Wilshut et al. 1995).

2.4.2. Database B - Human Skin Dataset

The initial classification made was based on the type of the membrane employed. Specifically, a large database of 167 compounds was developed first. There were 70 compounds in the human skin dataset, 43 compounds in the mouse skin dataset, 36 compounds in the rat skin dataset and 18 compounds in the silicone membrane dataset. The decision to collect data for human, rat and mouse skin respectively was mainly due to the fact that such data were widely available in the literature. Human skin would be expected to yield the best correlation with *in vivo* conditions but, because human skin is variable and difficult to obtain, it was possible that the use of rat and mouse skin as well as artificial membranes e.g. silicone, could provide

more reproducible data. Mouse and rat skin were included in this project, as both have been widely used in studies designed to investigate diffusion of compounds through human skin, although the latter is known to be less permeable than mouse and rat skin (Vecchia & Bunge 2005). When relevant papers were selected and values recorded, the data obtained using the same type of membrane were grouped together and treated as one set. In order to limit the inter-laboratory variation existing within the data, a second, more refined database, Database C, was constructed.

For the construction of Database B compounds used had low molecular weight (less than 600 Da) and log P values between -4.30 and 6.79. Specifically, in the human skin dataset comprising of 70 compounds, the largest-sized molecule was hydrocortisone 21-methyl-pimelate of 518.65 Da molecular weight whereas the largest log P value was that of methanol (4.78) and the smallest was that of raffinose (-4.30). The mouse skin dataset with 43 compounds included prednisolone pentadecanoate of 584.84 Da molecular weight; log P values ranged between -3.10 and 6.79. In the rat skin dataset with 36 compounds the biggest molecular weight was 504 Da and log P values went up to 3.86. Finally, the silicone dataset, with the fewest compounds (only 18), included hydrocortisone 21-hexanoate as its largest molecule with a weight of 460.61 Da and a log P value range between -0.86 and 4.48 (Appendix 2).

2.4.3. Database C - Human Skin Dataset

This dataset comprised 145 compounds and 269 K_p values derived from specific experimental conditions. A series of subgroups (Groups) were assembled; one of these ensured that data were derived under the same (specified) experimental conditions; other subgroups ensured similarities were maintained whereas others had fewer similarities. Data were grouped together according to these common similarities, which are all described in the following sections. In some studies where the K_p value was not determined previously in the reported literature, it was either calculated by dividing J ($mgcm^{-2}h^{-1}$) by C ($mgml^{-1}$) or when the initial concentration or flux were missing a request for the information was made to the corresponding author. In most of the cases the authors kindly provided this missing information. All human skin subgroups (Groups A1-A24) are summarised in Appendix 5.

2.4.3.1. Group A1: Ideal Human Skin Dataset

Group A1 might provide data that are most appropriate for model development because the adopted acceptance criteria used for this group refer to experiments which mimic the *in vivo* situation as closely as possible. These criteria were also suggested by OECD 2004b, c (Skin Absorption Test Guidelines), which were written to guide scientists to harmonise the *in vitro* methodologies. Specifically, for this group, membranes from the abdominal region of thickness varying from 0.2 to 0.5 mm were employed. Additionally, only data from infinite dose experiments were accepted using either neat compounds, if the compound was liquid at room temperature, saturated solutions in water, different grade propylene glycols, physiological buffers or even ethanol and methanol solutions ($\leq$ 10%) as application mediums. Furthermore, only flow-through cells were employed at an

exposure time of 24-48 h and temperature of 32 °C at the surface of the skin, generated by maintaining a temperature of 37 °C in the water bath. The use of radiolabelled test substances, HPLC and GC analysis were all acceptable analytical methods. Finally, with regards to the receptor fluid, only experiments using normal saline, isotonic buffer saline solution and HEPES-buffered Hanks´ balanced salt were accepted, whereas for lipophilic compounds, the use of bovine serum albumin (4%) or PEG 20 (6%) was deemed to be acceptable.

2.4.3.2. Group A2: The Effect of Skin Thickness

The acceptance criteria for this group (Appendix 5 – Group A2) were the same as those in Group A1. The only difference was in the thickness of membrane used. Specifically, data derived using full-thickness skin were included in Group A2, giving a wider range of experimental conditions used for the K_p determination.

2.4.3.3. Group A3: The Site of Human Skin / Abdominal and Breast Regions

This group (Appendix 5 – Group A3) was the same as Group A2. The only difference was in the site of application. Studies using skin obtained from the breast area as well as from the abdominal region were also included in the dataset, in addition to full thickness data.

2.4.3.4. Group A4: The Site of Human Skin / Various Regions

This group (Appendix 5 – Group A4) was the same as Group A2. The only difference was in the site of application. In addition to full thickness data in the dataset, experimental parameters from studies using skin obtained from various regions of the human body were also included. This group consisted of 28 compounds (46 K_p values).

2.4.3.5. Group A5: The Effect of the Apparatus Employed

This group (Appendix 5 – Group A5) was the same as Group A2. The only two differences between Group A2 and Group A5 were in the cell types employed (static / flow-through) and in the sites of application (in Group A2 only abdomen skin was employed whereas in Group A5 a mixture of skin types was used). Instead of using flow-through systems, the data were derived by using static cells only. This group consisted of 12 compounds for which their corresponding 13 K_p values were recorded.

2.4.3.6. Group A6: Flow-Through Cells / Abdominal and Breast Regions

This group (Appendix 5 – Group A6) was the same as Group A5. The only difference was in the site of application. Specifically, the data were derived from experiments using the breast area as well as that from the abdominal region. It consists of 15 K_p values corresponding to 14 chemicals.

2.4.3.7. Group A7: Flow-Through Cells / Various Regions

This group (Appendix 5 – Group A7) was the same as Group A6. The only difference was that all types of different skin thickness and various sites were employed over an extended study period of 24-72 h. It includes 46 K_p values of 26 compounds.

2.4.3.8. Groups A8 to A10: The Effect of Temperature

This group (Appendix 5 – Groups A8-A10) consisted of all the compounds, 145 compounds (269 K_p values), found in the human dataset. There are no specific acceptance criteria for this group of compounds and, thus, all experimental conditions were allowed in this dataset. All permeability coefficients were classified according to the temperature in the water bath during experiments (Table 2.3). Specifically, Group A8 corresponds to K_p values having being derived at temperatures between 25 and 32 °C (location not reported), Group A9 at 32 °C (temperature at skin surface) and Group A10 at 37 °C (temperature at water bath).

2.4.3.9. Group A11: The Effect of the *in Vitro* Cell Systems / Flow-Through Cells

Even though several comparative studies have suggested that there are no differences in skin permeability measurements using static and flow-through cells (Clowes et al. 1994), it is important to differentiate the experiments that use static cells to those using the flow-through systems. All other experimental conditions were deemed acceptable and used in this dataset. The Group A11 (Appendix 5 – A11) consists of all compounds, 56 in total (96 K_p values) where their corresponding K_p values were derived when the flow-through cell was employed. Group A11 differs from Group A1 because in the former there are no constraints being applied to the rest of the experimental factors involved, such as in skin thickness, temperature etc.

2.4.3.10. Group A12: The Effect of the *In Vitro* Cell Systems / Static Cells

Group A12 consisted of all compounds, 96 in total (165 K_p values) where their corresponding K_p values were derived when static cells were employed. This group (Appendix 5 – Group A12) is similar to Group A5, with the only difference being that no other constraints were applied to any of the other parameters under question. All the data in Group A12 were derived using human skin data in flow-through apparatus, in contrast those allocated to Group A11, when human skin data in static apparatus was used.

2.4.3.11. Groups A13 to A15: The Effect of the Receptor Fluid

These groups (Appendix 5, Groups A13 - A15) comprised of data derived using 64 compounds (121 K_p values) from experiments employing buffer solution (Group A13) as a receptor fluid, 22 compounds (24 K_p values) using water (Group A14) as a receptor fluid, and 79 compounds (145 K_p values) using a

combination of both buffer solution and water (Group A15) as a receptor fluid. For Groups A13-A15 and Group A1 the only parameter in common is the receptor fluid (buffer solution, water or both) employed. All the other parameters are different, since in Groups A13 to A15 no further constraints in the experimental criteria have been applied.

2.4.3.12. Group A16: Human Skin Dataset and Group A17: Elimination of Duplicates

Group A16 (Appendix 5, Group A16) consisted of 269 K_p values derived from compounds with a range of physicochemical properties. It contained all human skin data and therefore cannot be related to any of the other groups. In Group A16 there were a number of compounds with more than one value of K_p. These were rationalised to one value for each compound in Group A17 (145 K_p values). The elimination criteria were based on the experimental parameters employed for the K_p determination. Specifically, the K_p obtained under experimental conditions that tended to be similar or close to the 'ideal' experimental conditions (Group A1) were selected. The molecular weight (MW) of the chemicals in this dataset varies from 18.02 Da (water) to 793.86 Da (erioglaucine) and lipophilicity from hydrophilic molecules (minimum log P = 4.47 for glyphosate) to highly lipophilic (maximum log P = 8.39 for DEHP).

2.4.3.13. Group A18: The Elimination of Borax, Erioglaucine and Epikote XY4000

Group A18 consisted of 37 chemicals retrieved from the Flynn dataset, several others from Patel et al. (2002a), as well as further molecules from the EDETOX database. Also, borax, erioglaucine and epikote XY4000 were eliminated due to the fact that some of their descriptors could not be defined (e.g. SP, MPt, Ha, etc.) It is similar to Group A17, with the only difference being the elimination of these three compounds.

2.4.3.14. Group A19: The Addition of Seven Pig Skin Data

Group A19, consisted of the above-mentioned 142 compounds (Group A18) plus with some additional molecules reported by Moss et al. (2006). These latter additional seven compounds were inserted into the second dataset. Since there was a relatively low amount of data in the human database (Database C), which comprised 142 compounds, it was decided to add 7 other measurements taken under specific well controlled experimental conditions but unfortunately using pig skin. Even though pig skin differs from human skin in terms of lipid composition, pig is the closest species to human and therefore it presented the best alternative.

2.4.3.15. Group A20: The Ionisation Effect

In order for the percentage of ionisation to remain constant during every experiment, the receptor solution should be maintained at the same pH as the donor solution. Many experiments reported in the scientific literature do not declare the pH (in either the receptor and donor solutions). However, for the purpose of this

study, the percentage of ionisation existing within data in the human skin dataset was calculated using the following Equation 2.2:

$$\% \text{ ionised} = 100 / 1+10^{[\text{charge (pH-pKa)}]} \quad \text{(Equation 2.2)}$$

where the charge was 1 for bases and -1 for acids.

Group A20 was derived from Group A15. Log D for the remaining compounds could not be measured.

2.4.3.16. Group A21: Static and Flow-Through Cells: Elimination of Duplicates

In Group A21, static and flow-through cell data were combined, providing a group of 36 compounds. All duplicate values were eliminated. No other experimental constraints were applied to the data.

2.4.3.17. Groups A22 to A24: The Effect of Lipophilicity on Human Skin Data

As described earlier (Section 2.3.2.3.1), human skin data were divided into four groups, depending on the lipophilicities of the molecules involved. Group A22 was developed by collecting 12 molecules from the first group, Group A23 was developed by collecting 12 compounds from the second group, whereas the final one, Group A24, was created by selecting 11 compounds from the third group of Section 2.3.2.3.1.

2.4.4. Rat Skin Dataset

This dataset comprised data obtained for 77 compounds but employing 147 different log K_p values. As with the development of the human skin datasets, some datasets depended upon similar experimental conditions being defined whereas in other datasets there were fewer experimental conditions that were maintained constant. All rat skin datasets are summarised in Appendix 6. The following datasets were assembled.

2.4.4.1. Group B1: Ideal Rat Skin Dataset

Group B1, as shown in Appendix 6 – Group B1, consists of chemicals with K_p values derived from the most reliable and consistent experimental data. The acceptance criteria for this group were to employ membranes from the dorsal region of thickness within the range 0.2-0.5 mm. Additionally, only data from infinite dose experiments were accepted using either neat compounds if the compound was liquid at RT, saturated solutions in water, different grade propylene glycols, physiological buffers or even ethanol and methanol solutions ($\leq$10%) as application mediums. Furthermore, both flow-through and static cells were employed at a variety of temperatures. Finally, with regards to the receptor fluid, only experiments using normal saline, isotonic buffer saline solution and HEPES-buffered Hanks´ balanced salt were used,

whereas for lipophilic compounds, the use of bovine serum albumin (4%) or PEG 20 (6%) was deemed to be acceptable.

2.4.4.2. Group B2: The Effect of Skin Thickness

In this dataset the inclusion / exclusion criteria were the same as those in Group B1 with the only difference being in that the data in Group B1 (which was derived using split thickness skin) were combined with other data obtained using full-thickness skin.

2.4.4.3. Group B3: The Effect of Static Cells

This dataset comprised data that were collected adhering to the experimental conditions specified for Group B2 except that only static cells were employed for the *in vitro* measurements. It includes 23 K_p values corresponding to 9 chemicals.

2.4.4.4. Group B4: The Effect of Receptor Fluid

Group B4 (55 K_p values from 43 compounds) contained data obtained from experiments that employed a range of receptor fluids, namely: normal saline, isotonic buffer saline solution, HEPES-buffered Hanks´ balanced salt solution, bovine serum albumin (4%) and PEG 20 (6%). The only common parameter that Group B4 and Group B1 had was the use of the same receptor fluids. For Group B4, no other experimental constraints were applied.

2.4.4.5. Group B5: The Effect of Various Receptor Fluids

This group contained all the rat skin data available in Database C. No experimental restrictions were applied, including the receptor fluids employed. It consisted of 147 K_p values, corresponding to 77 compounds.

2.4.4.6. Groups B6 to B7: The Effect of Various Receptor Fluids

This subgroup consisted of compounds where the permeability coefficients were measured under various experimental conditions. All permeability coefficients were classified according to the temperature used either to the skin or in the water bath during the experiments. Data for the compounds in Group B6 comprised 40 K_p values derived from 25 compounds from experiments in which the temperature in the water bath was recorded to be between 30-32°C. Data for the compounds within Group B7 (56 K_p values from 33 compounds) were derived from experiments in which the temperature in the water bath was recorded to be 37 °C.

2.4.5. Mouse Skin Dataset

The mouse skin dataset consists of 47 compounds and 144 K_p values. All mouse skin datasets are summarised in Appendix 7. Mouse skin data were divided into the following groups:

2.4.5.1. Group C1: Ideal Mouse Skin Dataset

Group C1, as shown in Appendix 7 – Group C1, consists of chemicals with K_p values derived from the most reliable and consistent experimental data. The acceptance criteria for this group were to employ membranes from abdominal / dorsal region of full thickness. Finally, only flow-through cells were employed at a variety of temperatures. Finally, with regards to the receptor fluid, a wide range of receptor fluids was deemed to be acceptable. This group contained only 9 K_p values.

2.4.5.2. Group C2: The Site of Mouse Skin

This group includes data, which were obtained using the conditions outlined for Group C1 except that only data gained using skin derived from the abdominal region of the mouse were included. Also, both static and flow-through systems were included in the list. It was composed of 29 compounds (72 K_p values).

2.4.5.3. Group C3: The Site of Mouse Skin / Dorsal Region

As for Group C2, this subgroup also included data derived from both static and flow-through systems but, in contrast to Group C2, the data were comprised of those obtained from experiments where the skin under investigation was selected from the dorsal region of the mouse. It was composed of 24 compounds (67 K_p values).

2.4.5.4. Groups C4 and C5: The Effect of Temperature

Group C4 comprised 16 compounds (26 K_p values) where the data were obtained from experiments conducted in a water bath set at 37 °C. An additional dataset (Group C5) comprised of 18 compounds (66 K_p values), where the data were obtained from experiments in which the temperature was not provided. There were no further restrictions for the rest of the experimental conditions employed in both groups. As a result, it does not resemble any of the previous groups.

2.4.5.5. Group C6: No Experimental Restrictions.

This group contained all the mouse skin data available in Database C. No experimental restrictions were applied, including the receptor fluids employed. It consisted of 114 K_p values, corresponding to 47 compounds. Group C6 includes Group C4 and C5 together with the additional 22 K_p values existing in Database C.

2.4.6. Pig Skin Dataset

Due to the relatively few number of experiments that have been conducted with pig skin, the dataset was not further subdivided and, thus, the data that were assembled were derived under a variety of different experimental parameters. It consists of 21 compounds (35 different K_p values). However, all experiments were performed at 37 °C (water bath). All pig skin datasets are summarised in Appendix 8.

2.4.7. Membranes (Silastic Membranes and Skin Equivalents) Dataset

This dataset involves the inclusion of silicone membranes, together with skin equivalents, such as Graftskin™, Skinethic™ and Testskin™. It comprised the permeability coefficients of 21 compounds obtained with 39 K_p values. Again, due to the small amount of available data in the literature, Group E was not further subdivided into smaller and more specific groups. All the experimental data were obtained at 32 °C (at the surface of the skin). All synthetic skin datasets are summarised in Appendix 9.

2.4.8. Species Effect

This group comprised of compounds that were included both in the human skin dataset as well as in a dataset termed 'the rodent skin dataset,' which was the combined rat and mouse skin datasets. Specific chemicals existing in both datasets were included in the dataset and the rest of the compounds were eliminated. All experimental conditions were deemed to be acceptable during this analysis and no constraints were applied. Therefore, for each existing compound, two K_p values were incorporated into the dataset, one that was determined from *in vitro* experiments using human skin and the other using rodent skin. The group contained 54 compounds with 108 K_p values.

2.4.9. Summary of Datasets

Table 2.3 summarises all the groups existing within the total assembled database. Specifically, the experimental restrictions employed and the relevant membrane used in each group are detailed:

Table 2.3. Assembled groups existing in Database C showing the different membranes and experimental conditions employed.

Groups	Membrane employed	Experimental restrictions	No of compounds included in the groups	No of K_p values included in the groups	Appendix
A1	Human	Ideal experimental conditions (Section 2.4.3.1).	11	13	5
A2	Human	Ideal experimental conditions (Section 2.4.3.2) and full thickness data.	11	18	5
A3	Human	Ideal experimental conditions (Section 2.4.3.3), full thickness and data obtained from abdominal and breast sites.	20	27	5
A4	Human	Ideal experimental conditions (Section 2.4.3.4), full thickness and data obtained from various sites.	28	46	5
A5	Human	Ideal experimental conditions (Section 2.4.3.5), full thickness and data obtained when static cells were employed.	12	13	5
A6	Human	Ideal experimental conditions (Section 2.4.3.6), full thickness, data obtained when static cells were employed and data obtained from abdominal and breast sites.	14	15	5
A7	Human	Ideal experimental conditions (Section 2.4.3.7), full thickness and data obtained when static cells were employed and data obtained from various sites .	26	46	5
A8	Human	Temperature range (location not reported): 25-32 °C (Section 2.4.3.8).	12	13	5
A9	Human	Temperature range on skin surface: 32 °C (Section 2.4.3.8).	25	39	5
A10	Human	Temperature range in water bath: 37 °C (Section 2.4.3.8).	66	115	5
A11	Human	Flow-through cells (Section 2.4.3.9).	56	96	5
A12	Human	Static cells (Section 2.4.3.10).	96	165	5
A13	Human	Buffer solutions (Section 2.4.3.11).	64	121	5
A14	Human	Water employed as vehicle (Section 2.4.3.11).	23	24	5
A15	Human	Receptor Solution: Combination of buffer solution and water (Section 2.4.3.11).	79	145	5
A16	Human	No experimental restriction (Section 2.4.3.12).	145	269	5
A17	Human	All data. Duplicate values were eliminated (Section 2.4.3.12).	145	145	5
A18	Human	Elimination of borax, erioglaucine and epikote XY4000 (Section 2.4.3.13).	142	142	5
A19	Human	The addition of seven pig skin data Section 2.4.3.14).	149	149	5
A20	Human	Ionisation effect (Section 2.4.3.15).	20	20	5
A21	Human	Static / Flow-through cells. Duplicate values were eliminated (Section 2.4.3.16).	36	36	5
A22	Human	Low lipophilicity (Section 2.4.3.17).	12	12	5

Groups	Membrane employed	Experimental restrictions	No of compounds included in the groups	No of K_p values included in the groups	Appendix
A23	Human	Medium lipophilicity (Section 2.4.3.17).	12	12	5
A24	Human	High lipophilicity (Section 2.4.3.17).	11	11	5
B1	Rat	Ideal rat experimental conditions (Section 2.4.4.1).	4	13	6
B2	Rat	Ideal rat experimental conditions (Section 2.4.4.2) and full thickness data.	25	32	6
B3	Rat	Static cells employed (Section 2.4.4.3).	9	23	6
B4	Rat	Specific classes of receptor fluids were employed (Section 2.4.4.4).	31	55	6
B5	Rat	All kinds of receptor fluids were employed (Section 2.4.4.5).	77	147	6
B6	Rat	Temperature effect (location not reported): 30-32 °C (Section 2.4.4.6).	25	40	6
B7	Rat	Temperature effect in water bath: 37 °C (Section 2.4.4.6).	33	56	6
C1	Mouse	Full thickness skin, obtained from abdominal / dorsal region, both static and flow-through cells were employed (Section 2.4.5.1).	5	9	7
C2	Mouse	Various experimental conditions employed, but in terms of site only abdominal region data were used (Section 2.4.5.2).	29	72	7
C3	Mouse	Various experimental conditions employed, but in terms of site dorsal region data were used (Section 2.4.5.3).	25	67	7
C4	Mouse	Temperature effect in water bath: 37 °C (Section 2.4.5.4).	16	26	7
C5	Mouse	Temperature in water bath not given (Section 2.4.5.4).	17	66	7
C6	Mouse	No experimental restrictions (Section 2.4.5.5).	47	114	7
D	Pig	No experimental restrictions due to limited data (Section 2.4.6).	20	35	8
E	Membrane	No experimental restrictions due to limited data (Section 2.4.7).	21	39	9
F	Human versus rodent	No experimental restrictions (Section 2.4.8).	110	55	10

With regards to the 'ideal' subgroup (Group A1), the number of compounds employed was 11. Both caffeine and testosterone were recorded as having two different K_p values in the dataset. The use of such strict criteria to screen data indicated that this might not be an approach that could be used in QSPR development, when the resultant dataset was so restricted in number. In general, the size of independent variables depended on the size of samples (n). The minimum requirement for a valid model was that there should be at least 10 error degrees of freedom, such that n-k-1 is larger than 10, where k is the number of independent variables (Topliss & Costello 1972). So for Group A1 where N = 11, even if the number of independent variables is limited to just one, there still would be a problem while performing

regression analysis. It is clear that it would have been desirable to have more compounds included in this dataset in order to have a greater confidence in the proposed model.

With regards to Group A2, as shown in Table 2.3, eighteen (18) K_p values were provided and these correspond to 11 compounds (Appendix 5). More than one K_p value is given again for caffeine (2 K_p values) and testosterone (7 K_p values). Additionally, regarding Group A3, twenty seven (27) K_p values were determined and these corresponded to the 20 compounds. Similarly, caffeine (2 K_p values) and testosterone (7 K_p values) existed in more than one K_p values. Furthermore, as shown in Table 2.3, there were 46 K_p values of Group A4 corresponding to a variety of chemicals. Appendix 5 shows in detail, which compounds exist in each group and for which chemicals more than one K_p values exist. Regarding Group A5, the subgroup was made by combining Group A1 data (ideal data) together with the full thickness data and with the data obtained when static cells were employed. The 13 K_p values which resulted corresponded to codeine, coumarin, etorphine, griseofulvin (2 K_p values), nicotine, n-nitrosodiethanolamine, salicylic acid, testosterone, methyl parathion, cimetidine, adenosine and deoxyadenosine. This group differed from Group A12 in terms of involving ideal data together with static cell data, as opposed to Group A12 where all type of experimental data were employed together with the static cell data. By employing a wider range of data in Group A12, more K_p values were included. Additionally, in order to determine the effect of the two different types of diffusion apparatus employed in the measurement of K_p on the quality of the developed QSPRs, two different models were developed. The first one included measurements performed using static cells (Group A12) whilst the second comprised measurements performed using flow-through cells (Group A11). All the other experimental parameters were deemed to be acceptable.

In addition, the effects of compound ionisation play a critical role in skin permeation process and should therefore be considered when QSPRs are to be constructed. In Section 2.4.3.15, the pH values of the compounds applied in aqueous solutions to the human skin dataset were not reported and hence these were calculated using the Henderson-Hasselbach equation. However, the data derived for some compounds that were included in Group A20 were obtained from studies in which the solutions employed were buffered. Table 2.4 indicates the data, which were obtained for compounds under either buffered or non-buffered conditions. Nevertheless, irrespective of the buffer capacity of each solution used, the pH in each case was calculated using the Henderson-Hasselbach equation. The compounds in this dataset (n = 20) were all ionised more than 50%.

Table 2.4. Group A20 – Reports of buffered solutions.

Chemicals – conducted in buffered solutions	Chemicals - conducted in non buffered solutions
adenosine	benzoic acid
coumarin	chlorpyrifos
diazinon	clotrimazole
lidocaine	DDT
methotrexate	dimethylformamide
morphine	doxycycline HCL
prochloraz	flufenamic acid
salicylic acid	ketoprofen
sufentanil	nicotinic acid
	nimesulide
	pirimicarb

With regards to rat skin data and specifically to Group B1, only 13 permeation coefficients were measured according to the 'ideal' rat data experimental conditions. The following compounds employed two or more values within the data group: dodecyl decaethoxylate (2 K_p values), dodecyl monoethoxylate (2 K_p values), 2-phenoxyethanol (5 K_p values) and theophilline (4 K_p values). For Group B2, 32 K_p values available in literature were included in this dataset, out of which benzyl acetate (2 K_p values), fenoxapropethyl (3 K_p values), 2-phenoxyethanol (2 K_p values) and theophylline (4 K_p values) were incorporated, having two or more reported values of K_p.

Table 2.3 presents data for the compounds belonging to Group B5 (40 K_p values – 25 compounds) that were derived from experiments, in which the temperature at skin surface was recorded to be between 30 °C and 32°C. Additionally, data for the compounds within Group B6 (56 K_p values – 33 compounds) were derived from experiments in which the temperature in the water bath was recorded to be 37 °C. In both cases, the temperature at the skin surface remained the same, approximately 32 °C.

With regards to the mouse skin data (Group C1), only nine K_p values were found in the literature that were measured under the 'ideal' mouse data conditions and these corresponded to only five compounds. These were atenolol, o-cresyl glycidyl ether (oCGE), dodecyl glycidyl ether (C12GE), epikote YX4000 and 1,6-hexanediol diglycidyl ether (HDDGE). In order to increase the number of compounds included in the dataset, the experimental parameters were widened, reducing the limitations imposed upon data selection. This necessitated encompassing data obtained under a greater variety in the experimental conditions. Furthermore, it is acknowledged that due to the relatively few number of experiments that have been conducted with pig skin and other membranes, the corresponding datasets were not further subdivided and, thus, the data were gathered under a variety of different experimental parameters.

Regarding the membrane dataset (Appendix 9), it must be pointed out that for skin equivalents, such as Graftskin™, Skinethic™ and Testskin™, data were grouped together with silicone membrane data. Human skin equivalents (HSEs) are bio-engineered substitutes composed of primary human skin cells (keratinocytes, fibroblasts and / or stem cells) and components of mainly collagen (Zhang & Michniak-Kohn 2012). Consequently, it would be expected (as shown in Appendix 9), that HSEs would provide smaller K_p values compared to the corresponding ones obtained via silicone membranes. Nevertheless, due to the small size of data available in the literature, under specific experimental conditions for both silicone membranes and HSEs, these two major groups were being combined and considered as one.

This dataset included silicone membranes and skin equivalents (HSEs). It comprised the permeability coefficients of 21 compounds obtained with 39 K_p values. Similarly, due to the small amount of available data in the literature, Group E was not further subdivided into smaller and more specific groups. All the experimental data were obtained at 32 °C at the surface of the skin. All synthetic skin datasets are summarised in Appendix 9.

Finally, in order to examine the effects of lipophilicity the human skin log P values were divided into three distinct categories each containing 12 K_p values of 12 compounds. These comprised the 'low log P value'

category (log P < 1) – Group A22, the 'medium log P value' category (1 < log P < 3) – Group A23 – and the 'high log P value' category (log P > 3) – Group A24.

2.5. CONCLUSION

In this chapter, a series of datasets was assembled. The data gathered for them were obtained under defined conditions. Due to the various sources of data available in the literature, the data needed to be grouped according to common experimental conditions with a view to using these in turn to seek to validate current and develop new models. Using K_p values derived from various experimental sources would result in algorithms of smaller predictive capacity as a consequence of errors introduced by inter- and intra-laboratory variation in experimental procedures. Therefore, the data was screened carefully and classified into different subgroups. All groups were constructed according to specific criteria, which eliminated K_p values when their method of derivation was unknown. At the same time, similar experimental methodologies were brought together, demonstrating the importance of using K_p values determined under similar experimental conditions. It must be pointed out that the most ideal dataset to be used for future model development was considered to be Group A1. However, small datasets such as A1 cannot be very descriptive and may generate uncertainties. This lack of adequate 'ideal' data should encourage scientists to measure new data under carefully-controlled, agreed conditions and should also trigger researchers to use these databases in order to test the validity of current models and develop novel QSPRs. Nevertheless, before conducting new, well controlled experiments (Group A1), it is important to evaluate current models by manipulating the larger-scale databases (Databases B and C, Sections 2.3.1 and 2.3.2) using linear (Chapter 3) and non-linear (Chapter 4) statistical methods.

Chapter Three

Evaluation of Existing QSPRs

3.1. BACKGROUND AND RATIONALE

In Chapter 2 the data collected from the literature were grouped into a series of specific datasets / subgroups. It is therefore appropriate to seek to examine current QSPR models with those datasets / subgroups.

3.1.1. Data Quality: The Need to Apply Data Acceptance Criteria

The rationale for establishing data acceptance criteria is to provide a framework to enable *in vitro* percutaneous absorption and distribution data from all available sources to be grouped together on a sound basis. Consequently, according to the acceptance criteria set in Section 2.3, various datasets were generated. First, it was planned to validate one of the current datasets existing in Database A, for example the most cited one, the Flynn dataset, by comparing the resulting regression coefficient to that produced by Potts and Guy (1992) (Evaluation A). This validation process was deemed necessary in order to identify reproducibility issues between researchers before proceeding with the actual evaluation of the current models by using more controlled data. However, such validation was necessarily selective, since it lay outside the principal aims and objectives of this chapter. It was then planned to carry out a second study (Evaluation B) employing Database B as described in Section 2.3.1 (Appendix 2). The data acceptance criteria applied in the latter case involved the employment of the permeability coefficient values that were derived experimentally rather than computationally. The resulting regression coefficients obtained between the predicted and the actual experimental values were then recorded and compared. The experiments were then further classified according to the membrane employed during their conduct. However, as already discussed in Chapter 2, to further limit any uncertainties that might exist within the data, extended screening of the compounds was conducted in terms of further refining the data acceptance criteria, with the aim of providing a more efficient QSPR evaluation (Evaluation C). Database C (the final consolidated database) is summarised in Appendix 3.

3.1.2. Outliers

Many researchers in the past, as discussed in Sections 1.1 and 2.1, excluded compounds while developing QSPRs and these were commonly termed 'outliers.' There are a number of reasons for the occurrence of outliers (Cronin 2005), including perhaps the operation of a different mechanism of action for the compounds concerned. If this is not recognised, it can lead to the development of a model with low predictive ability. The most simplistic approach is to consider that outliers do not exist and to remove them from the subsequent data analysis, but this can be viewed as malpractice. Only when a clear scientific rationale is provided, should the outliers be taken away from the dataset and the resulting model might then yield improved statistics.

3.1.3. Data Manipulation and Statistical Analysis

Data manipulation in multicentred analyses has effects similar to traditional regression analyses, where addition or subtraction of a constant or a compound from a database, based on a scientific rationale,

does not change the relationships in the data (Kraft et al. 2004). As discussed in Section 2.4.3.12, in order to construct the most relevant datasets, many K_p values were eliminated from the datasets because they did not meet the acceptance criteria set for each developed dataset. Consequently, by applying linear regression analysis to the manually manipulated data, as described in Chapter 2, the relative importance of each constructed dataset might be determined. Calculating the regression coefficients of the models developed using data from the specific subgroups would demonstrate the variability of the data within each subgroup. Data manipulation only makes it possible to exploit the portion of data which is most useful in modelling the specific observed relationship (Hartwig & Dearing 1979). Regression analysis (Section 1.8.3) is the statistical tool employed in the data manipulation process. It was employed in the current chapter as a simple statistical technique seeking to relate a dependent variable to one or more independent variables. The statistical parameters, associated with 'the goodness of fit' of a regression-based QSPR, are the squared multiple correlation coefficient adjusted for degrees of freedom (R^2); the cross-validated (leave-one-out) multiple correlation coefficient (R^2CV); the standard error of the fit (S); and the F statistic. Furthermore, t values and associated probabilities (p) should be available for individual variables in the regression analysis and the number of compounds used in the model (n) should be reported (further details concerning statistical measures are available elsewhere (Livingstone 1995; Livingstone & Cronin 2004). The p-value is the probability that the descriptor is there by chance and a p-value of ≤ 0.05 is generally regarded as significant, although it should be noted that p-values have little meaning if the descriptors are selected from a large pool. However, as already discussed in Section 1.8.3, due to its linearity, it is not clear if regression analysis would be a suitable technique for the development of QSPRs (Degim et al. 2003).

3.2. AIMS AND OBJECTIVES

3.2.1. Aims

Databases containing measured and well defined skin absorption data are a key first step in the development of QSPR models, which might improve the understanding of the dermal absorption process for chemicals. Accordingly, the aim of the chapter was to evaluate already existing QSPRs via screened and critically reviewed data, with the view of indicating their limitations and of highlighting the need to develop novel models.

3.2.2. Objectives

The objective of the work was to provide a comprehensive review and evaluation of mathematical models for predicting skin permeability. The current mathematical models for predicting skin permeability were compared and any deficiences existing in the models were identified and reviewed.

3.3. METHODS

3.3.1. Evaluation A – Database A

As noted previously in Section 2.3.1, the first section of Database A (Appendix 1) was the Flynn dataset. The publication by Flynn of a large heterogeneous dataset was a significant milestone in developing QSPRs for the prediction of skin permeability. Analysing the Flynn dataset, Potts and Guy (1992) observed up to 30% variability in the experimental data and they did not investigate the role of outliers or other statistical anomalies. Since the Potts and Guy (1992) equation was proposed, more accurate log P data, using computational methods like EPIWIN software, have become available and a more thorough QSPR analysis is warranted. Regression analysis of the complete Flynn dataset was conducted using the SPSS (version 1.0 for MS Windows, SPPS Inc., Chicago, 2006) software for validation purposes.

The most commonly used and most cited QSPR models were reviewed and their statistical validity was recorded. Specifically, the Potts and Guy (1992), Barratt (1995b), Cronin et al. (1999), revised Robinson (1995) and revised Brown and Rossi (1995) models were all reviewed and their corresponding regression coefficient value was recorded. The datasets upon which these models were developed are shown in Table 3.1.

Table 3.1. A selection of past QSPR models illustrating sample size (number of compounds), correlation coefficient (R^2) and the source of the data used.

Model	N	R^2	Experimental data source
Potts & Guy (1992)	93	0.67	Flynn (1990)
Barratt (1995b)	60	0.90	Flynn (1990)
Cronin et al. (1999)	107	0.86	Flynn (1990) + Health Canada (WHO 2006)
revised Brown and Rossi (1995)	99	0.96	Wilshut et al. (1995)
revised Robinson (1995)	119	0.51	Wilshut et al. (1995)

3.3.2. Evaluation B – Database B

For Evaluation B, all data were derived from sources published in the literature but the membrane employed during the conduct of the experiments had to be identified. The impact that different species may have on the permeation profile of a compound has already been discussed in Chapter 1 (Section 1.2.3.1).

Database B is analysed in detail in Section 2.3.2. Specifically, all data were combined together according to the membrane employed during the permeability experimentation. It consists of 167 compounds containing 70 compounds in the human skin dataset, 43 compounds in the mouse skin dataset, 36 compounds in the rat skin dataset and finally 18 compounds in the silicone membrane dataset. All data presented in these datasets are summarised in Appendices 11-14.

3.3.2.1. Selection of Independent Variables

It is well documented that many physicochemical properties influence the rate of absorption or flux across the skin. As this study involved large compound datasets, it was a prerequisite that the independent variables should be readily available for each compound. The molecular weight (MW), log P and the solubility parameter (SP) are key relevant independent variables pertinent to the process of dermal absorption. Several studies have suggested that the SP may predict the absorption of solutes across the skin and hence the reason for the inclusion of such a parameter in this study was to determine whether any correlation exists between the SP of a number of diverse compounds and their dermal absorption in human (Sun et al. 2010b). Fedors' group contribution method (1974) was chosen because the only knowledge needed in order to calculate SP is the drug structure; furthermore, values for large numbers of functional groups are available in the literature. Values taken from literature sources may be checked, introducing control into the compound datasets generated for each skin or membrane type.

3.3.2.2. Quality Check of the Data Employed in the Dataset

SPs were calculated using Fedors' group contribution method, although initially many of these SP values were obtained from literature sources, which stated that Fedors' group contribution methods had been used. However, despite this first check to eliminate the possibility of using SPs calculated or derived by other methods, two different reference sources may have quoted different values for the same compound. Therefore, in order to limit any variation, the solubility parameter was recalculated using the group contributions in order to introduce a quality check and to ensure first that the values being used in this analysis are derived by Fedors' method and second that correct units of $(cal/cm^3)^{1/2}$ values were used (Fedors 1979). An example of such a quality check is shown for the calculation of SP for salicylic acid (Table 3.2).

Table 3.2. Fedors' method for calculating the solubility parameter (SP) of salicylic acid.

Functional groups	Δu (cal/mol)	ΔV (cm^3/mol)
1 x 6 membered ring	250	16.00
3 x C=C (conjugated bonds)	1200	-6.60
4 x CH=	4120	54.00
1 x COOH	7830	27.00
1 x OH	5220	13.00
Total	18620	103.40

Ghafourian et al. (2001) reported a SP value of 13.13 $(cal/cm^3)^{1/2}$ for salicylic acid; whereas the corresponding calculated value obtained from the data in Table 3.2 for a quality check was 13.41 $(cal/cm^3)^{1/2}$, having been derived from Equation 2.1. As a result, it was decided to manually calculate all SP values, for all compounds available in the dataset.

3.3.2.3. Models Used for the Evaluation Process

It was decided to employ the Potts and Guy (1992), the Cronin et al. (1999), the revised Brown and Rossi (1995) and the revised Robinson (1995) models for establishing the 'fit' of Database B by determining the

regression coefficient value when the predicted values obtained were plotted against the experimentally derived values. Specifically, all models were reanalysed using the updated Database B.

3.3.2.4. Exclusion of Anomalous Data from Datasets

Since the selected experimental data were to be used to evaluate the models, it was decided to exclude certain compounds from the dataset. For example, the Potts and Guy (1992) model was devised using compounds having a log P in the range between -3.0 and 5.0 and a molecular weight smaller than 500 Da. In other words, this model was reanalysed using Database B but excluding compounds with log P values outside the limits that were originally specified by Potts and Guy (1992).

3.3.3. Evaluation C – Database C

For Evaluation C, it was decided to employ the same QSPRs as those used in the evaluation process B, with the addition of an extra model, the Barratt (1995b) model. The membrane / skin types used here as well as the independent variables employed, were exactly the same as those used for the evaluation of Database B. The only difference was the inclusion of the melting point, which provides an indication of the extent of hydrogen bonding, as a parameter in the Barratt (1995b) model. It consists of 284 compounds. Specifically, 129 compounds in the human skin dataset obtained from human Group A18 (Section 2.4.3.12), 35 compounds in the mouse skin dataset obtained from mouse Group C dataset (Section 2.4.5), 77 compounds in the rat skin dataset (Group B dataset, Section 2.4.4), 20 compounds in the pig skin dataset (Group D dataset, Section 2.4.6) and 21 compounds in the membrane dataset (Group E dataset, Section 2.4.7). All data presented in these subgroups are summarised in Appendices 15-19. In all cases, molecules with molecular weight bigger than 500 Da and of log P values bigger than 5 were eliminated from the analyses.

3.3.3.1. Search for the Data Employed in the Database Construction Process

Permeability coefficients were obtained from reported specific experiments, which fulfilled detailed specific protocols. A minimum set of criteria were required to describe all experimental protocols such as type of skin, vehicle, dose, concentration, area of exposure, exposure time, receptor fluid, diffusion cell used, method of membrane preparation, analysis, study length and temperature.

3.3.3.2. Database Construction – Database C

A more stringently controlled database, which included parameters derived under more strictly defined experimental conditions, was also developed. Some log K_p values existing in the Flynn dataset show large variations, possibly due to the experimental conditions that prevailed during the generation of the data. Indeed, some are simply not permeability coefficients at all, but rather describe the disappearance of the drug molecule from a solution. Also, in

some cases the log K_p values are probably not experimentally determined but are artificial data generated by employing a previously established QSPR model (Neumann et al. 2008). For some compounds more than one permeability coefficient value was reported in the Flynn dataset and such duplicate values were eliminated, the value selected being based upon the quality of the reported experimental procedures employed. Furthermore, for certain compounds, only the basic experimental conditions under which the experiments were conducted were reported. Specifically, factors such as pH, occlusion, temperature of the receiver fluid etc. were not always reported. In other cases, the differences in K_p values were greater than one log unit suggesting that there were large interlaboratory variations in such measurements. For the evaluation of past and current QSPRs, either one representative data point for each molecule was selected or the multiple data points were combined in a reasonable way. Although numerous experimental investigations have been performed since the publication of the Flynn (1990) dataset, similar and especially better-documented collections of log K_p values are hard to find. As already discussed in Section 2.3.3, Database C consisted mostly of compounds where the K_p values were determined under specific experimental conditions. Database C consisted of 24 groups (Groups A1-A24) according to the experimental parameters employed. For the purpose of the thesis, Database C was thought to be the database with the most experimental restrictions and was therefore designated as the most 'pure' database in terms of quality.

Database C, as described in Section 2.3.3, was developed by combining all data existing in the EDETOX database with that published by Wilshut et al. (1995), Patel et al. (2002a) and all other *in vitro* data published in the literature up to 2008. The difference between Database C and B is that Database C contains compounds where the corresponding permeability coefficients have been derived under specific experimental conditions. Database C can be seen in Appendices 3 and 15 to 19 and is fully analysed in Chapter 2.

3.3.3.3. Exclusion of Anomalous Data from Datasets

As discussed earlier in Section 1.4.2, drugs of medium lipophilicity will have reasonable penetration rate through the stratum corneum. Furthermore, highly lipophilic substances (log P > 5) can pass easily through the stratum corneum and are generally too water-insoluble to pass through the remaining sublayers and enter the bloodstream. Additionally, molecular size is an important factor in membrane permeation (Cussler 1997). As a result, compounds were removed from Database C based on the above scientific rationale. Specifically, molecules with molecular weight (MW) greater than 500 Da and of log P values greater than 5 were eliminated from Database C (Section 3.3.3). As a second step, narrower log P values were employed to further investigate the influence of the lipophilicity on the permeability process. Specifically, the log P range was narrowed to accept values between -3.0 and 3.0. In other words, in order to reanalyse the current models, Database C was employed by excluding compounds with log P values outside the limits that were originally specified and explained by the Potts and Guy (1992) model. The effect of MW was not investigated at this thesis. Lipophilicity was considered to be a more important predictor for skin permeability. However, the original acceptance criteria that excluded compounds of MW exceeding 500 Da were applied. There was no further classification of compounds with respect to their size.This is an issue that could be further investigated in the future.

3.3.3.3.1. Human Skin

Group A18 (142 compounds) was used as a reference group in the human skin Database C. It was chosen because it offers the best balance between controlled data and number of compounds required to produce a robust algorithm. Thirteen compounds were eliminated from Group A18 (Appendix 5) because they had log P values outside the accepted log P range (-3 < log P < 5). A further 32 compounds were removed from Database C when the log P range was limited further to between -3 and 3. The molecular weight range remained the same (MW ≤ 500 Da). The 45 compounds that were eliminated from Group A18 are all summarised in Table 3.3.

Table 3.3. 'Outliers' removed from the human skin dataset: restrictions in log P values.

Name	Log P	Name	Log P
glyphosate [a]	-4.47	ethinyl estradiol [b]	4.00
meperidine [b]	3.03	diclofenac [b]	4.02
4-n-butylaniline [b]	3.10	doxycycline HCL [b]	4.05
naproxene [b]	3.10	fentanyl [b]	4.05
n-hexyl nicotinate [b]	3.10	diethyl squarate [b]	4.07
ethanol [b]	3.12	prochloraz [b]	4.13
ketoprofen [b]	3.12	lindane [b]	4.26
ortexolone [b]	3.15	chlorpyrifos [b]	4.66
chloroxylenol [b]	3.25	nonane [b]	4.76
testosterone [b]	3.27	flufenamic acid [b]	4.88
2-phenylphenol [b]	3.28	dodecyl glycidyl ether (C12GE) [a]	5.01
butyl paraben [b]	3.47	dibutylphthalate [a]	5.11
thymol [b]	3.52	epikote YX4000 [a]	5.19
4-n-pentylaniline [b]	3.59	terbinafine [a]	5.81
sufentanil [b]	3.62	clotrimazole [a]	6.26
progesterone [b]	3.67	DDT [a]	6.79
parathion [b]	3.73	cannabinol [a]	7.23
bisphenol A diglycidyl ether (BADGE) [b]	3.84	linoleic acid [a]	7.51
diazinon [b]	3.86	Δ-tetrahydrocannabinol (THC) [a]	7.60
pregnenolone [b]	3.89	cannabidiol [a]	8.01
NTX-3 heptanoate (HEP-NTX) [b]	3.92	DEHP [a]	8.39
ibuprofen [b]	3.97	disodium octaborate tetrahydrate [a]	28.00
β-estradiol [b]	3.97		

[a] -3 < log P < 5

[b] -3 < log P < 3

3.3.3.3.2. Mouse Skin and Pig Skin

The compounds listed in Table 3.4 were excluded from the initial mouse skin dataset (Group C, Section 2.4.5), since they possess physicochemical properties outside the accepted values, i.e. log P > 3 or log P < 0. The acceptance criteria were adjusted according to the nature and number of *in vitro*-derived data available in the literature using mouse and pig skin.

Table 3.4. 'Outliers' removed from the mouse skin dataset.

Name	Log P	Name	Log P
erioglaucine	-1.50	prednisolone 21-nonanoate	5.58
methanol	-0.63	prednisolone 21-tridecanoate	6.02
dodecyl glycidyl ether (C12GE)	5.01	prednisolone 21-tridecanoate	6.02
prednisolone 21-octanoate	5.09	prednisolone 21-decanoate	6.07
epikote YX4000	5.19	prednisolone 21-decanoate	6.07
trifluralin	5.31	prednisolone 21-pentadecanoate	6.79
prednisolone 21-undecanoate	5.54	prednisolone 21-pentadecanoate	6.79
prednisolone 21-undecanoate	5.54	decabromodiphenyl oxide (DBDPO)	12.11
prednisolone 21-nonanoate	5.58	decabromodiphenyl oxide (DBDPO)	12.11

Additionally, etorphine, 17α-hydroxyprogeasterone, deoxycortisone, alachlor, TDCPP, progesterone, bisphenol A diglycidyl ether, diethyl squarate and prednisolone 21-heptanoate were also removed from the initial mouse skin dataset because their physicochemical properties were outside the set range of values (MW < 500, -3 < log P < 3).

For the assembly of the pig skin dataset, only pentachlorophenol was eliminated from Database C (Appendix 8) due to its log P value being greater than 5.

3.3.3.3.3. Rat Skin

The compounds listed in Table 3.5 were removed from the initial rat skin dataset due to their physicochemical properties being outside the set range of values (MW < 500, log P < 5). Again, the acceptance criteria were adjusted according to the nature and number of *in vitro*-derived data available in the literature using rat skin.

Table 3.5. Compounds removed from the rat skin dataset.

Name	Log P	Name	Log P
erioglaucine	-1.50	terbinafine	5.81
dodecyl glycidyl ether (C12GE)	5.01	dodecane	6.23
dibutylphthalate	5.11	clotrimazole	6.26
epikote YX4000	5.19	tridecane	6.73
decane	5.25	DDT	6.79
mefenamic acid	5.28	linoleic acid	7.51
undecane	5.74	DEHP	8.39

While validating the models by using the rat skin dataset, the following 23 compounds were also removed from the initial rat skin dataset due to the fact that their physicochemical properties were outside the desired range of values (MW < 500, log P < 3). Consequently, due to this further refinement, benzene, xylene (dimethyl benzene), 4-n-butylaniline, ketoprofen, nimodipine, naphthalene, clebopride, testosterone, 2-phenylphenol, domperidone, 4-n-pentylaniline, dinoseb, bisphenol A diglycidyl ether (BADGE), felodipine, nicardipine, nifedipine, butyl salicylate, 4-n-hexylaniline, haloperidol, dodecyl decaethoxylate, dodecyl monoethoxylate, nonane and fenoxapropethyl terbinafine were all eliminated and a second rat skin dataset was developed.

3.3.3.4. Evaluations A, B and C of Existing QSPRs

To evaluate the existing mathematical models mentioned earlier in this chapter, the following template (Table 3.6) was used, where the data were grouped according to the type of membrane used. However, the experimental conditions used to derive the data were taken into account and did indeed vary. Even in Database C, the variation existed, but to a smaller extent.

Table 3.6. Template of experimental permeability coefficients and drug properties.

No.	Name	MW	Log P	SP $(cal/cm^3)^{1/2}$	Log K_p (cmh^{-1})	K_p (cmh^{-1})

The independent variables were substituted into each of the selected models to generate predicted permeability coefficients. The residuals between the experimentally derived log K_p and the 'predicted' value were then stored in the compound databases using Microsoft Excel® software (Table 3.7). The predicted log K_p (cmh^{-1}) values were obtained from mathematical models after substitution of the relevant physicochemical parameters, whereas the experimental log K_p (cmh^{-1}) values were obtained using a wide range of literature sources (Appendices 11-19).

Table 3.7. Template of compound dataset containing predicted values and residuals.

Name	Log K_p (exp) (cmh^{-1})	Log K_p (pred) (Potts & Guy) (cmh^{-1})	Log K_p (exp) - Log K_p (Potts & Guy) (cmh^{-1})

In the same manner, the equations associated with the other models (revised Robinson 1995, revised Brown and Rossi 1995, Cronin et al. 1999 and Barratt 1995b) were incorporated into Microsoft Excel spreadsheets in order to obtain the values of the predicted permeability coefficients.

3.3.3.5. Data Manipulation via Statistical Analysis Methods

For the purpose of the project, the regression coefficient value (R^2) and standard error(s) were calculated for each model developed. All statistical analyses and data interrogation were carried out using the SPSS software package (version 1.0 for MS Windows, SPPS Inc., Chicago, 2006). Linear regression analysis was used to produce QSPRs. Analysis of residuals from the regression equations was used to assess the validity of each equation derived from data developed under specific experimental conditions. Duplicates from each dataset were eliminated so that regression analysis could be applied. The compounds that were discarded from the datasets were eliminated due to their K_p values having being derived from experiments mimicking the *in vivo* situation to a lesser extend.

For the purpose of data manipulation, the effect of ionisation was taken into consideration by determining the % ionisation in each study under investigation, using Equation 2.2 in Section 2.4.3.15. The pH value of the solution was not reported for the majority of journals in the literature. As a result, it was measured by using the Henderson-Hasselbalch equation, in acids (Equation 1.15) and in bases (Equation 1.16), which describes the derivation of pH as a measure of acidity. The equation is also useful for estimating the pH of a buffer solution and finding the equilibrium pH in acid-base reactions (it is widely used to calculate the isoelectric point of proteins).

3.4. RESULTS AND DISCUSSION

As already discussed in Section 3.1.1, the data upon which the existing models were developed contain both a high degree of experimental error as well as results for a number of compounds where the conditions used to derive them were not reported and are hence 'unknown'. Specifically, with regards to the Flynn dataset, large variations exist in the reported K_p values, possibly due to the experimental conditions, while some K_p values are simply not permeability coefficients at all, but rather describe the disappearance of the drug molecules from a solution (Neumann 2008). Additionally, from the 94 compounds available in the Flynn dataset, only 37 K_p values have been derived from experimental conditions, which have been fully reported in the literature. For the development of the Cronin et al. (1999) model, additional data were obtained from the regulatory reports of Health Canada. The majority of these data, available in the Flynn and Cronin et al. (1999) datasets, were excluded from both Databases B and C, since the experimental conditions used to derive those were not fully or not at all reported. As a result, data were screened in order to develop more stringently-controlled datasets that included parameters derived under more strictly-defined experimental conditions. These data were then used in the re-evaluation process of the current models.

A summary of the degree of statistical fit to the different QSPR models is shown in the results section in Table 3.8. The acceptance ranges for inclusion of data and the designated experimental conditions under which the data were derived are also given.

Table 3.8. Human skin: Statistical fit to the respective models obtained using the specified different datasets.

Model	Origin database	Data range	R^2	Experimental conditions
Potts and Guy (1992)	Database A (Flynn 1990)	18 < MW < 765 -3 < log P < 6	0.67 (n = 93)	Human Skin. No specific experimental restrictions. Appendix 1.
Potts and Guy (1992)	Database B	46 < MW < 489.61 -2.25 < log P < 5.49	0.40 (n = 63)	Human skin. See Database B criteria – Appendices 2 and 11.
Potts and Guy (1992)	Database C	500 < MW -5 < log P < 5	0.17 (n = 129)	Human Skin. See Database C criteria – Appendices 3 and 15.
Potts and Guy (1992)	Database C	500 < MW -3 < log P < 3	0.28 (n = 97)	Human Skin. See Database C criteria – Appendices 3 and 15.
revised Brown and Rossi (1995) model	Database A (Wilshut et al. 1995)	18 < MW < 765 -3 < log P < 6	0.96 (n = 99)	Human Skin. Specific experimental restrictions were recorded (temperature, occlusion, receptor medium, design of the cell, anatomical locations). Appendix 1.
revised Brown and Rossi (1995) model	Database B	46 < MW < 518.65 -2.25 < log P < 5.49	0.11 (n = 66)	Human skin. See Database B criteria – Appendices 2 and 11.
revised Brown and Rossi (1995) model	Database C	MW < 500 -5 < log P < 5	0.14 (n = 130)	Human Skin. See Database C criteria – Appendices 3 and 15.
Cronin et al. (1999) model	Database A [Flynn (1990) + Health Canada. Steroids, propylene chloride, estriol, hydrocortisone, atropine etorphine, digitoxin and sucrose were eliminated.]	30.03 < MW < 390.56 -1.51 < log P < 4.78	0.86 (n = 107)	Human Skin. Derived from a variety of sources, therefore there is variability in the exact methodologies. No specific experimental restrictions. Appendix 1.
Cronin et al. (1999) model	Database B	46 < MW < 489.61 -2.25 < log P < 5.49	0.42 (n = 63)	Human skin. See Database B criteria – Appendices 2 and 11.
Cronin et al. (1999) model	Database C	500 < MW -5 < log P < 5	0.26 (n = 129)	Human Skin. See Database C criteria – Appendices 3 and 15.
Cronin et al. (1999) model	Database C	500 < MW -3 < log P < 5	0.33 (n = 97)	Human Skin. See Database C criteria – Appendices 3 and 15.
revised Robinson (1995) model	Database A (Wilshut et al. 1995)	18 < MW < 765 -3 < log P < 6	0.51 (n = 99)	Human Skin. No specific experimental restrictions were recorded (temperature, occlusion, receptor medium, design of the cell, anatomical locations). Appendix 1.
revised Robinson (1995) model	Database B	46 < MW < 489.61 -2.25 < log P < 5.49	0.43 (n= 63)	Human skin. See Database B criteria – Appendices 2 and 11.
revised Robinson (1995) model	Database C	500 < MW -5 < log P < 5	0.25 (n = 129)	Human Skin. See Database C criteria – Appendices 3 and 15.
revised Robinson (1995) model	Database C	500 < MW -3 < log P < 3	0.35 (n = 97)	Human Skin. See Database C criteria – Appendices 3 and 15.
Barratt (1995b) model	Database A (Flynn 1990 – excluded hydrocortisone derivatives)	18 < MW < 765 -3 < log P < 6	0.90 (n = 60)	Human Skin. No specific experimental restrictions. Appendix 1.
Barratt (1995b) model	Database C	500 < MW -5 < log P < 5	0.16 (n = 127)	Human Skin. See Database C criteria. Appendices 3 and 15.
Barratt (1995b) model	Database C	500 < MW -5 < log P < 3	0.21 (n = 97)	Human Skin. See Database C criteria. Appendices 3 and 15.

Human datasets from both Databases B and C were assembled and the above models were reassessed by re-examining the statistical fit using these databases. The selection of compounds was based on a narrower range of log P and molecular weight (MW) values. The resulting regression coefficients indicated a greater statistical fit. In addition to the human skin dataset, the rat skin, mouse skin, pig skin and synthetic membrane dataset evaluations were all determined and recorded. Table 3.9 shows the statistical fit of the Potts and Guy (1992) model, when different datasets, derived from different species, were employed. The experimental restrictions were more or less similar, with the only difference being the membrane employed.

Table 3.9. Rat skin, mouse skin, pig skin and membrane: statistical fit of the Potts and Guy (1992) model obtained using the specified different databases.

Model	Origin database	Data range	R^2	Experimental conditions
Potts and Guy (1992)	Database B	130.01 < M < 360.04 -2.14< log P < 4.12	0.56 (n = 33)	Rat skin. See Database B criteria – Appendix 13.
Potts and Guy (1992)	Database C	500 < MW -5 < log P < 5	0.13 (n = 63)	Rat skin. See Database C criteria – Appendix 17.
Potts and Guy (1992)	Database B	32 < MW < 486.55 -1.83 < log P < 4.39	0.05 (n = 39)	Mouse skin. See Database B criteria – Appendix 12.
Potts and Guy (1992)	Database C	18.02 < MW < 472.62 -1.56 < log P < 4.6	0.64 (n = 35)	Mouse skin. See Database C criteria – Appendix 16.
Potts and Guy (1992)	Database B	94.11 < MW < 460.61 -0.86 < log P < 4.48	0.79 (n = 18)	Membrane. See Database B criteria – Appendix 14.
Potts and Guy (1992)	Database C	122.1 < MW < 354.5 0.16 < log P < 6.79	0.135 (n = 21)	Membrane. See Database C criteria – Appendix 19.
Potts and Guy (1992)	Database C	MW < 354.5 log P < 5.81	0.13 (n = 19)	Pig skin. See Database C criteria – Appendix 18.

3.4.1. Evaluation A – Flynn Dataset

A full statistical analysis was reperformed using the full Flynn dataset, as part of Database A, and indeed the statistical fit of data to the Potts and Guy (1992) equation (Equation 1.21) has been confirmed to be comparatively poor. Potts and Guy (1992) did observe that up to 30% variability in the experimental data was to be expected, however they did not investigate the role of outliers or other statistical anomalies. Since the Potts and Guy (1992) equation was proposed, more accurate log P data, obtained using the KOWWIN software, have become available and a more thorough QSPR analysis was warranted. Regression analysis of the complete Flynn dataset was conducted using the SPSS (version 1.0 for MS Windows, SPPS Inc., Chicago, 2006) software for validation purposes. By taking into consideration the log P values calculated using the KOWWIN software (Appendix 1) and the SPSS software, Equation 3.1 resulted.

$$\text{Log } K_p \text{ (cmh}^{-1}\text{)} = -2.62 + 0.569 \log P - 0.00543\ MW \qquad \text{(Equation 3.1)}$$

$N = 93$, $R^2 = 0.61$, $S = 0.84$

The coefficients of the descriptors and the constants in the model do not alter markedly when the original Potts and Guy (1992) equation (R^2 = 0.67) is compared with Equation 3.1 (R^2 = 0.61). This indicates a stable model even though the statistical fit is not particulrly good. Apart from the fact that current models are not only limited in part because of the quality of the data used to develop them, variations can be brought due to the different software employed for the determination of the corresponding parameters used (KOWWIN, ALOGP, MLOGP, ChemAxon etc.). Log P values employed in the development of the original Potts and Guy (1992) model did not fluctuate beyond 2 log units, when compared to the corresponding log P values calculated computationally via the KOWWIN software. Consequently, it is apparent that only 'ideal' experimental data and validated softwares for input determination should be employed in the development and subsequent evaluation of QSPR models (Ryman-Rasmussen et al. 2006). Hence, care should be taken when selecting the appropriate statistical tool and appropriate software for the determination of the predictors while developing new QSPRs.

3.4.2. Evaluations B, C

3.4.2.1. Human Skin – Database B

When Database B (Section 2.3.2) was employed, the four mathematical models displayed varying performances in estimating the permeability coefficients of compounds across human skin. Specifically, the correlation coefficient derived from the Potts and Guy model (1992) was found to be R^2 = 0.40 (n = 63), from the Cronin et al. (1999) model was found to be R^2 = 0.42 (n = 63), from the revised Brown and Rossi (1995) model was found to be R^2 = 0.11 (n = 66) and from the revised Robinson (1995) model was found to be R^2 = 0.43 (n = 63). All these four models displayed very poor performances, especially compared to the original ones. They also required specific experimental conditions under which they could be employed validly. Such model-specific assumptions may, for example, relate to the particular requirements of the compound and these may include physicochemical parameters such as molecular weight (MW) or partition coefficient ranges. Clearly, should compounds be without these limits, it may be expected that very poor permeability estimates will result. The Potts and Guy (1992) model was originally developed using 93 of the compounds from the Flynn (1990) dataset and produced a reasonable correlation (R^2 = 0.67) between predicted and reported log K_p values. However, when used with Database B, as assembled in the current study, the same correlation proved to be poorer (R^2 = 0.40). The Potts and Guy (1992) model developed using Database B was found to overestimate the permeability coefficients for 37 compounds from a total of 63 in the dataset and underestimate the coefficients of the remaining 26 compounds. These results were unexpected, since using a smaller data subset derived from the Flynn dataset should mean a smaller diversity in the data, giving a more robust model with higher regression coefficient and consisting of data derived from clearly-specified methodologies. However, by taking a smaller subset of 29 compounds from Database B, with a log P ranging between 0.25 and 4.59 and MW between 46.00 and 392.5 Da, a markedly improved correlation between experimental and predicted permeability coefficients was obtained (R^2 = 0.894), which was better than that produced originally when the Flynn dataset was employed. Thus, it can be concluded that the Potts and Guy

(1992) model is suitable for predicting the permeability coefficients of compounds having these narrow physicochemical values. By limiting the values of the physicochemical properties of the molecules existing in the dataset and particularly by selecting compounds with log P values of smaller than 5, the statistical fit of the Potts and Guy (1992) model increased.

Furthermore, when Database B was applied to the revised Brown and Rossi (1995) model, the latter was established from the study of 66 compounds and the resulting correlation coefficient between experimentally-derived permeability coefficients and predicted values estimated was found to be really poor (R^2 = 0.11). Three more compounds were used since the model had no molecular weight contribution; therefore the acceptance criterion of MW < 500 was not applicable. The model overestimated the permeability coefficients of all but four compounds from a total of 66 in the human skin dataset. This model was particularly poor at estimating the permeability coefficients of very highly lipophilic compounds, possibly due to the fact that it neglected permeation through the water-containing epidermal layers, which may provide a barrier for some of the more lipophilic drugs (Wilschut et al. 1995).

When the human skin data taken from Database B were incorporated into the revised Robinson (1995) model, the latter demonstrated the best performance when used to predict permeability across human skin with a regression coefficient of 0.45 for the full database, Database B, as compared with the regression coefficient of 0.43 produced by applying Database B to the Cronin et al. (1999) model, and R^2 = 0.91 for a subset of 29 compounds. This subset of 29 compounds was taken for further evaluation using Database B with MW ranging between 46.00 and 392.5 Da and log P values between -0.25 and 4.59. The revised Robinson (1995) model, just like the revised Brown and Rossi (1995) model, assumes the stratum corneum to be a lipophilic / non-polar membrane.

The data assembled by Kirchner et al. (1997) were subsequently reanalysed by Cronin et al. (1999) and the resultant model designated as the Cronin et al. (1999) model. When the model was re-evaluated using the data assembled as Database B (Table 3.8), a plot of experimental log K_p against predicted log K_p produced a regression coefficient value of 0.42 (Appendices 2 and 11). The model overestimated the permeability coefficients of 20 compounds, whilst the permeability coefficients of the remaining 43 compounds in the dataset were underestimated. Thus, the Cronin et al. (1999) model generally tended to underestimate the permeability coefficients of the compounds in the human skin dataset. However, the Cronin et al. (1999) model proved to be more accurate than the Potts and Guy (1992) model when employed for predicting permeability across human skin (Table 3.8).

Therefore, it was found that all the above-mentioned mathematical models displayed very poor performances when used for estimating the permeability coefficients of compounds across human skin. It remains likely that this is due to the quality of the initial data upon which these models were developed in the first place. By introducing human data from Database B, as described in Section 2.3.2, it was expected that the models would provide a better estimate of the corresponding permeability coefficients. Nonetheless, a lower correlation coefficient was obtained and this might be due to the empirical constants being derived using all of the original data. Although more selective data were employed, obtaining new constants might lead to a better

correlation between actual and derived coefficients but this would probably require a reanalysis of the data. With respect to validation process B, a smaller dataset was used than that employed to derive the original equation and this is likely to influence the final statistical analysis. The current QSPRs were developed from specific datasets, comprising specific compounds. When some of the compounds were eliminated and new ones were added, as described in Section 2.3.1, the models were found unable to accommodate the nature of the new data (Database B), meaning that the models cannot be expected to predict activities beyond the defined prediction range. Yet, before developing novel QSPRs, it was still considered of importance to re-evaluate the current models, but this time by using the designated 'best' dataset in terms of the quality of the experimental conditions under which Database C was derived.

3.4.2.2. Human Skin – Database C

When all models were reanalysed using human skin data from Database C (Section 2.3.2), the correlation between the predicted and the experimental log K_p values was found to be poor once more, confirming that current QSPRs work only for a specific set of compounds of certain physicochemical range. The regression coefficients (R^2) derived from the Potts and Guy (1992) (n = 129), Cronin et al. (1999) (n = 129), revised Brown and Rossi (1995) (n = 130), revised Robinson (1995) (n = 129) and Barratt (1995b) models were 0.17, 0.26, 0.14, 0.25 and 0.16 respectively. Specifically, the Potts and Guy (1992) model overestimated the permeability coefficients of 66 compounds out of a total of 129 in Database C (Appendix 15), whereas the remaining 63 compounds were underestimated. On the other hand, by taking a subset of 97 compounds (Appendix 15) from Database C with a log P ranging between -3 and 3 and a MW above 500 Da, an improved correlation between experimental and predicted permeability coefficients was obtained (R^2 = 0.28). As shown in Table 3.8, the Potts and Guy (1992) model displayed the worst performance (R^2 = 0.17) when the most refined data (Database C, Section 2.3.2) were employed, compared to the performance measured by Potts and Guy (1992) when Database B and the Flynn dataset were used (R^2 = 0.67). As the restrictions in the experimental conditions upon which permeability data were produced increased from Database A (i.e. the Flynn dataset) to Database C, a poorer regression coefficient resulted by using the same equation. Clearly, the models were tested against different data in terms of number, structure and physicochemical properties of the compounds. As indicated above, they were developed using original data and for this reason the correlation coefficients were optimised. When more selective and refined data were used, the original equations would appear to require re-evaluation.

Similarly, the revised Brown and Rossi (1995) model, established from the study of 130 compounds from Database C, also demonstrated a poor correlation (R^2 = 0.14) between experimentally derived permeability coefficients and predicted values estimated by the model (Table 3.8). In Table 3.8, it is shown that in the revised Brown and Rossi (1995) re-evaluation analysis 130 compounds were used rather than 129, as employed by the other models (except Barratt's 1995b model). This was due to the fact that one additional compound with MW above 500 Da was used, since the revised Brown and Rossi (1995) model does not employ molecular weight in its prediction. This model demonstrated the worst performance when used to

predict permeability across human skin. It overestimated the permeability coefficients of all but four compounds from a total of 130 in the human skin dataset. For these compounds, the revised Brown and Rossi (1995) model failed to predict suitable permeability coefficients, particularly again (as when Database B was employed) for very-highly-lipophilic compounds.

The revised Robinson (1995) model demonstrated the second best performance when used to predict permeability across human skin (R^2 = 0.25) using the full dataset (130 compounds from Database C) and a higher correlation (R^2 = 0.35) when a subset of 97 compounds were extracted from Database C and employed. This subset of 97 compounds was taken from the human skin dataset and had MW smaller than 500 Da and log P values between -3 and 3. The Cronin et al. (1999) model demonstrated the best performance when used to predict permeability across human skin (R^2 = 0.26) when the full database (Database C) was employed but this was improved when a subset of Database C with 97 compounds was used (R^2 = 0.33). When Database C was used, this model overestimated the permeability coefficients of 88 compounds, whilst those of the remaining 41 compounds were underestimated. Thus, the Cronin et al. (1999) model tended to overestimate the permeability coefficients of the compounds in the human skin dataset.

Finally, the correlation coefficients derived from the Barratt (1995b) model were also very poor (R^2 = 0.16) when either the full dataset (n = 127) or a subset of 97 compounds (R^2 = 0.21) were employed (Appendix 15). In Table 3.8, it is shown that 127 compounds were used in the Barratt (1995b) re-evaluation analysis rather than 129 in the other models (except the revised Brown and Rossi 1995 model). This was due to the fact that two compounds (4n-pentylaniline and h-hexyl nicotinate) were eliminated because their melting point values were not available in the literature. The model overestimated the permeability coefficients of most compounds (n = 106), whilst the remaining permeability coefficients (n = 21) were underestimated.

3.4.2.3. Other Membranes – Databases B and C in Existing Models

Four mathematical models were evaluated using Database B. These were re-evaluated (alongside an additional, fifth model – the Barratt 1995b model) using Database C. Datasets of experimentally measured skin permeability for 66 compounds (Database B – human skin dataset, Appendix 11) and 129 compounds (Database C – human skin dataset, Appendix 15) have been compiled and used to test all models. The results, as shown in Table 3.8, indicated that the use of the revised Robinson (1995) model produced the best prediction of permeability when Database B was employed and the Cronin et al. (1999) model produced the best prediction of permeability when Database C was employed. Both models provided high correlation coefficients between estimated and experimental log K_p values. The revised Robinson (1995) model was derived theoretically based on the existence of alternative or aqueous polar pathways across the skin. Respective datasets were constructed for the rest of the skin membranes, i.e. for the mouse skin, rat skin etc. (Table 3.9). By comparing Evaluation B and C results when membranes other than human skin was employed (Table 3.9 and Appendices 12, 13, 14 and 16, 17, 18, 19), it was observed that, as the number and the variety of compounds in the database was increasing, the resultant correlation coefficients derived from each model

tended to decline. A higher statistical fit might possibly have been anticipated when the data obtained under defined conditions were employed but the more variable data produced the better the correlation. As the number of the compounds in the database tended to increase, their diversity within the data increased as well, indicating the limitations that these models have in predicting permeability coefficients of compounds when compounds with an extensive range of physicochemical properties is used.

This contradiction was observed in the evaluation of all QSPRs when all kinds of skin were employed, suggesting that the original equations may need revision precisely because they were founded on data obtained under variable experimental conditions. The quality of each model was further assessed by determining the compounds that were poorly predicted by these linear models or did not fit the algorithm well. Such compounds are commonly termed 'outliers.' By introducing the concept of outliers in the model assessment process and perhaps by deleting them from subsequent analyses, it is possible that the statistical fit for each model could increase. However, the treatment of outliers has caused controversy among developers of QSPRs for decades (Ryman-Rasmussen et al. 2006). The most simplistic approach is to remove them and 'pretend' they do not exist, but this is not a good idea in the modelling process. To avoid this potential simplification, the complete dataset to be modelled was reported and any so-called 'outliers' were included in the analysis.

3.4.2.4. Mouse Skin Dataset

In addition to the data analysis carried out using human skin refined data, the Potts and Guy (1992) (Table 3.9), Cronin et al. (1999) and revised Brown and Rossi (1995) models were analysed using data derived from the mouse skin datasets (Appendices 12 and 16). When the mouse skin dataset taken from Database B (Appendix 12) was employed, all of the models displayed very poor performances in predicting permeability estimates across mouse skin with regression coefficient values equal to 0.05, 0.13 and 0.07 respectively (Table 3.9). Similar poor results were obtained when the mouse skin dataset taken from Database C was used (Appendix 16). Similarly, the Potts and Guy (1992), Barratt (1995b), Cronin et al. (1999), revised Brown and Rossi (1995) and revised Robinson (1995) models displayed very poor performances when used to predict estimates of permeability across mouse skin with regression coefficient values equal to 0.64, 0.22, 0.20, 0.02 and 0.15 respectively for 35 chemicals (see Appendix 16). All these correlations proved to be poorer than when the original datasets used to devise the original respective models (Database A) were employed (Table 3.8). All analyses using the equations relevant to the respective models predominantly overestimated skin permeability. In the case of the revised Brown and Rossi (1995) model, the log permeability coefficients of only 3 compounds out of the 35 were underestimated.

A number of published studies have used hairless mouse skin as a more readily available substitute membrane for human skin when conducting *in vitro* experiments. Although mouse skin exhibits some of the barrier properties characteristic of human skin, the specialised complex nature of human skin stratum corneum cannot be fully replicated (Moss et al. 2002). According to the findings of this analysis, the main problem with the Potts and Guy (1992) and Cronin et al. (1999) models was a consistent underestimation of

log K_p for almost every compound in the mouse skin dataset. The revised Brown and Rossi (1995) model displayed a combination of both underestimation and overestimation of permeability of specific compounds within the dataset, with the latter slightly dominating. Therefore, it was established that experimental permeability coefficients taken from literature sources were generally higher than the estimated values obtained using the previously developed models. These findings are in agreement with a previous report where it was proposed that the primary problem associated with the use of rodent skin as model for human skin is the overestimation of permeability compared to human skin (Friend 1992).

3.4.2.5. Rat Skin Dataset

Similarly, when the rat data obtained from Databases B and C (Appendices 13 and 17) were incorporated into the Potts and Guy (1992), Cronin et al. (1999) and revised Brown and Rossi (1995) models, the resultant correlation coefficients were very low. With regards to the rat data taken from Database B, the obtained regression coefficient values were 0.56, 0.59 and 0.27 respectively, while when the rat data from Database C were employed, the obtained regression coefficient values were 0.13, 0.19, 0.004 respectively (n = 21). Despite the poor predictions made when the currently selected models were applied, the performance of these models using rat skin closely resembles their performance when human skin was employed for permeability estimation purposes. In the current study, it was found that the Potts and Guy (1992) and Cronin et al. (1999) models are better for predicting permeability across rat skin, which appears to be a better mimic of human skin than hairless mouse skin (Patel et al. 2002a).

3.4.2.6. Pig Skin and Other Membranes Dataset

Table 3.9 shows that when the pig skin data obtained from Database C were employed, the Potts and Guy (1992) model displayed poor performance but similar to the one obtained when rat skin was used. Therefore, pig skin data were not included in Database B and no further QSPR evaluations were made. Additionally, when the silicone membrane data were combined with the LSE data (Database C), a much smaller regression coefficient was produced when the Potts and Guy (1992) model was employed (Table 3.9) compared to the Potts and Guy (1992) model regression coefficient obtained through silicone membrane data alone.

3.4.3. Data Manipulation

3.4.3.1. Manipulation of Human Skin Data

The current mathematical models that were selected for evaluation failed to provide satisfactory predictions for the permeabilty coefficients, when the refined Databases B and C (discussed in detail in Chapter 2) were employed. This means that these models have been developed to accomodate experimentally derived permeability coefficients for a large variety of compounds obtained using widely varying experimental conditions. As a result, there appears to be a need to develop new models, based on the most 'ideal' data

identified here, assembled in Database C. Therefore, data manipulation was conducted in Database C (Section 2.3.2) via the use of linear regression analysis in order to create more predictive models based on the controlled experimental data. As already discussed in Chapter 2, Database C consisted of 310 compounds. This database was further subdivided into five distinct datasets (Human skin dataset – Groups A1-A24, Rat skin dataset – Groups B1-B7, Mouse skin dataset – Groups C1-C6, Pig skin dataset – Group D and Synthetic membrane dataset – Group E). With a view to developing new linear algorithms via regression analysis, data manipulation was performed on the subsets (groups) of Database C (summarised in Table 2.3).

A series of regression analyses were performed using the data given in Appendix 5; in order to determine the permeability coefficient parameter, five dependent variables (molecular weight, Fedors' solubility parameter, partition coefficient, hydrogen bond acceptor and donor parameters) were generated. The R-squared type statistics indicated the goodness-of-fit in each case.

When regression analysis was conducted for Group A1 (Human skin, 'ideal' group), Equation 3.2 was produced:

$$\text{Log } K_p \text{ (cmh}^{-1}) = -0.482 + 0.017\ MW - 0.021SP - 0.3972 \log P - 0.339\ Ha - 0.25\ Hd \qquad \text{(Equation 3.2)}$$

$N = 11,\ R^2 = 0.66,\ S = 0.83$

where MW is the molecular weight, SP is the Fedors' solubility, log P is the partition coefficient, Ha is the hydrogen bond acceptor activity and Hd is the hydrogen bond donor activity.

The equation was produced through regression analysis. The usefulness of the above parameters and the reasons why these were chosen will be further discussed in Section 4.4.2. Molecular Weight and log P are the universally accepted indicators of permeability.

The above equation provided a good statistical fit to the data ($R^2 = 0.66$). The model developed explained 66% of the variance within the data with the rest remaining unknown. Given that 34% experimental variation in permeability data is not uncommon, the analysis suggests that the model completely describes the data. However, the number of compounds employed in the analysis was limited to eleven. For this reason, as already discussed in Chapter 2, more compounds should be included in this dataset, implying that more experiments employing the 'ideal' (i.e. tightly defined) conditions have to be performed.

Additionally, in order to determine the effect of the two different types of diffusion apparatus employed in the measurement of K_p on the quality of the developed QSPR, two different models were developed. The first measurement was performed using static diffusion cells (Group A12) whilst the second comprised measurements performed using flow-through diffusion cells (Group A11). For comparison reasons, from both groups (Group A11 and Group A12) the same number of compounds was selected. Specifically, the 25 compounds of similar physicochemical properties were employed for both groups and equations were derived by applying linear regression techniques to the data available. Once more, the same five dependent variables were used for K_p determination. The model which was developed from the data obtained using the static cell

apparatus provided higher regression coefficient (Equation 3.3) than the one obtained when the flow-through system was used (Equation 3.4).

$\text{Log } K_p \text{ (cmh}^{-1}\text{)} = -2.067 - 0.01425 \text{ MW} - 0.00972 \text{ SP} + 0.703 \log P + 0.39 \text{ Ha} - 0.032 \text{ Hd}$ (Equation 3.3)

$N = 25, R^2 = 0.43, S = 1.08$

$\text{Log } K_p = -2.88 + 0.0057 \text{ MW} + 0.024 \text{ SP} - 0.28 \log P - 0.56 \text{ Ha} - 0.086 \text{ Hd}$ (Equation 3.4)

$N = 25, R^2 = 0.24, S = 1.13$

When static cell and flow-through data were put together (Group A18), a separate dataset resulted with 36 different compounds (Appendix 5, Group A21), providing Equation 3.5.

$\text{Log } K_p \text{ (cmh}^{-1}\text{)} = -2.33 - 0.00154 \text{ MW} + 0.079 \text{ SP} - 0.0838 \log P - 0.16 \text{ Ha} - 0.085 \text{ Hd}$ (Equation 3.5)

$N = 36, R^2 = 0.12, S = 1.29$

A total of 14 compounds were eliminated when the datasets were grouped due to duplication. The resulting correlation coefficient was 0.12 indicating that the model which was developed by combining static and flow-through apparatus data exhibited a poorer correlation than the models developed using data from separate apparatus. Once more, increased variability in the data resulted in lower regression coefficient values.

Furthermore, variability in temperature control within the set up of an experiment is likely to act as a major source for interlaboratory variations. Different equations (Equations 3.6 and 3.7) were developed for Group A9 (32 °C on the skin surface) and Group A10 (37 °C in the water bath). The regression coefficient of the model resulting from the analysis of Group A10 was slightly higher ($R^2 = 0.39$, n = 24) than the one obtained from the analysis of Group A9 ($R^2 = 0.41$, n = 24).

$\text{Log } K_p \text{ (cmh}^{-1}\text{)} = -6.192 - 0.0026 \text{ MW} + 0.357 \text{ SP} + 0.265 \log P - 0.0088 \text{ Ha} - 0.404 \text{ Hd}$ (Equation 3.6)

$N = 24, R^2 = 0.41, S = 0.86$

$\text{Log } K_p \text{ (cmh}^{-1}\text{)} = -0.088 - 00056 \text{ MW } -0.082\text{SP} + 0.0412 \log P + 0.0466 \text{ Ha} - 0.352 \text{ Hd}$ (Equation 3.7)

$N = 24, R^2 = 0.39, S = 0.86$

The difference in the regression coefficient parameters obtained was found to be small, suggesting that both models explain the same percentage of variation within the respective data used to generate each equation. However, it is interesting that in order to get a similar regression coefficient, the integers employed in these equations are quite dissimilar. This might be due to the different nature of the data employed in each case.

Another important parameter that has to be considered during *in vitro* experiments is the choice of receptor fluid. When Group A13 (employing buffered solutions) was analysed and compared to data obtained from non-buffered solutions, the model developed using compounds from buffered solutions displayed the higher regression coefficient (R^2 = 0.34, n = 64) (Equation 3.8).

$$\text{Log } K_p \text{ (cmh}^{-1}\text{)} = -2.70 + 0.000259\ MW - 0.0037\ SP + 0.198 \log P - 0.197\ Ha + 0.0025\ Hd \qquad \text{(Equation 3.8)}$$

$N = 64,\ R^2 = 0.34,\ S = 0.88$

This indicated that data produced from buffered solutions are likely to prove more robust in model development than data obtained from all other types of receptor fluids. Buffered solutions might include less variation in the resulting K_p values, since the ionisation degree of the compounds in the solution under investigation would be minimised. As a result, more reliable data are produced, resulting in models with a greater statistical fit. By combining Groups A13 and A14, the resulting Group A15 provided the following equation with a regression coefficient of 0.37 (n = 79). Groups A13 and A14 had nine compounds in common. For the purpose of regression analysis, the duplicate values were eliminated, resulting to Group A15 having 79 compounds in total (Equation 3.9).

$$\text{Log } K_p \text{ (cmh}^{-1}\text{)} = -2.608 + 00009\ MW - 0.004\ SP + 0.2131 \log P - 0.294\ Ha + 0.06\ Hd \qquad \text{(Equation 3.9)}$$

$N = 79,\ R^2 = 0.37,\ S = 0.88$

As already discussed in Section 1.4.5, the effect of compound ionisation plays a critical role in the skin permeation process and, thus, it was taken into account during the current QSPRs construction. Group A20 consists of 20 compounds and the regression analysis performed between experimentally-derived K_p values and values derived from the developed model was found to be 0.52 (Equation 3.10).

$$\text{Log } K_p \text{ (cmh}^{-1}\text{)} = -4.11 - 0.00413\ MW - 0.06\ SP + 0.4680 \log D + 0.443\ Ha - 0.4856\ Hd \qquad \text{(Equation 3.10)}$$

$N = 20,\ R^2 = 0.52,\ S = 0.722$

As seen earlier in the chapter (Section 3.3.5), the pH values for many of the compounds existing in the human skin dataset were calculated using the Henderson-Hasselbach equation. Therefore, the pH was calculated from the

initial concentration of the applied solution together with the compound's dissociation constant. However, the data derived for some compounds, which were included in Group A20, were obtained in studies employing buffered solutions. Table 2.4 indicates the data, which were obtained for compounds under either buffered or non-buffered conditions. Nevertheless, irrespective of the buffer capacity of each solution used, the log K_p in each case was calculated using Equation 3.10. The compounds in this dataset (n = 20) were all ionised more than 50%. Consequently, it can be concluded that the majority of the compounds existing in datasets are ionised molecules.

Due to the limited size of the studies available in the literature, in which the pH or the initial concentration of the solution under investigation was reported, no more than 20 compounds were used for the analysis of Group A20. Even when the pH was eventually calculated for a variety of studies and the relevant log D values were determined (Section 1.4.2.2), the majority of these studies reported measurements in non-buffered solutions. Consequently, in order to avoid any possible uncertainty in the data available in the literature, a second ionisation model was also developed (Equation 3.12). This new linearly-developed model was based on the log D values reported by Avdeef (2003) as well as on some computationally-developed values. Specifically, 300 values of log P for neutral molecules (log P^N), of log P for ionised molecules (log P^I) and log $D_{7.4}$ of a variety of compounds were reported (Avdeef 2003). These values have been critically selected to represent high quality results, obtained since 1991 by using either Serious Analytical Instrument or pION software (www.pion-inc.com). Many of these constants were personally determined by Avdeef (2003), either experimentally or computationally. For the development of the second linear ionisation equation, an effort was made to calculate the log D values for the human data (Group A17, n = 145) of Database C. Log D was determined for only 33 out of 145 compounds (Appendix 22), by using the values reported by Avdeef and the additional, computationally-derived ones. In order to computationally determine log D values, the log P values for the ionised species are required. Since these are very limited in the literature, log D could not be calculated for the 145 compounds of Group A17.

By selecting the log D values for a range of chemicals where the log K_p values (determined via experiments using the human skin data obtained from Database C) have been reported previously (Section 2.3.2), the following two regression equations resulted. The first one (Equation 3.11) was developed by using two parameters only (log D and MW) whilst the second one (Equation 3.12) was generated by using five inputs (log D, MW, SP, Ha and Hd).

$$\text{Log } K_p \text{ (cmh}^{-1}) = -1.160 + 0.173 \log D - 0.008 MW \qquad \text{(Equation 3.11)}$$

$N = 33$, $R^2 = 0.44$, $S = 0.892$

$$\text{Log } K_p \text{ (cmh}^{-1}) = -0.551 + 0.046 \log D - 0.004 MW - 0.076 SP - 0.055 Ha - 0.308 Hd \qquad \text{(Equation 3.12)}$$

$N = 33$, $R^2 = 0.56$, $S = 0.822$

When comparing both log D equations (Equations 3.10 and 3.12), it can be seen that even though Equation 3.12 shows a similar fit of data (R^2 = 0.56) compared to Equation 3.10 (R^2 = 0.52), it has a larger standard error of estimation. From the total 33 compounds used to develop Equation 3.12, a percentage of 25% corresponded to compounds with high lipophilicity (log P > 4), whereas for the development of Equation 3.10, a smaller amount of compounds were highly lipophilic and would potentially remain in the outer layer of the skin.

The dataset (n = 33) used for the development of Equation 3.12 was shown to have 6 common chemicals with the dataset (n = 20) used for the development of Equation 3.10. When log D values of these 6 compounds that were determined experimentally were compared to the corresponding ones that were obtained computationally from the Avdeef report, 50% of the log D values (3 compounds only) were found to have close log D values (i.e. not fluctuating beyond 2 log P units). This means that a 50% confidence exists within the data for the remaining compounds in each dataset. For this reason, as well as for the limited number of studies determining the pH or even the initial concentration of the solution under investigation, Equation 3.12 was selected to be used as the reference ionisation model.

When all the linear models developed here were compared with those derived from the currently described models (Table 3.1), there were no improvements (Table 3.10). It can be seen that even though data obtained under better-controlled conditions were used in the newly-developed linear QSPRs, the resulting statistical fit was generally poorer due possibly to the increased diversity of compounds (in terms of physicochemical properties) included in each of the revised datasets.

Table 3.10. A selection of past linear QSPR models together with the currently developed ones illustrating sample size (number of compounds), correlation coefficient (R^2) and the source of the data used.

Model	N	R^2	Experimental data source
Potts and Guy (1992)	93	0.67	Flynn (1990)
Barratt (1995b)	60	0.90	Flynn (1990)
Cronin et al. (1999)	107	0.86	Flynn (1990) + Health Canada (WHO 2006)
revised Robinson (1995)	99	0.51	Wilshut et al. (1995)
revised Brown and Rossi (1995)	99	0.96	Wilshut et al. (1995)
Group A1 QSPR	11	0.61	'Ideal experimental conditions'
Static cell QSPR	25	0.43	Group A12
Flow-through cell QSPR	25	0.24	Group A11
Temperature 32 °C	24	0.41	Group A9
Temperature 37 °C	24	0.39	Group A10
Rec. fluid QSPR-buffer	64	0.34	Group A13
Rec. fluid QSPR-buffer & water	79	0.37	Group A15
Ionisation QSPR (1) Equation 3.10	20	0.52	Group A20
Ionisation QSPR (2) Equation 3.12	33	0.56	Avdeef (2003)

3.4.3.2. Manipulation of Other Membrane Data

Since it is commonly accepted that the type of membrane employed plays a significant role in K_p determinations, human, rat, mouse and pig skin as well as synthetic membrane datasets were analysed

separately and QSPRs were produced for each class of respective membrane. The regression coefficient was found to be higher for the pig skin dataset (R^2 = 0.71, Equation 3.13), demonstrating a superior statistical power in comparison to the mouse skin data (R^2 = 0.41, Equation 3.15) and to the rat skin data (R^2 = 0.30, Equation 3.14). When regression analysis was performed on the membrane dataset, the resulting standard error was found to be extremely high (S = 329.45). Therefore, the equation describing it was not taken into account in the thesis. For reasons of comparability, all the above datasets included the same number of compounds (n = 18).

$$\text{Log } K_p \text{ (cmh}^{-1}\text{)} = -1.49 - 0.023\,MW - 0.042\,SP + 1.053 \log P + 0.507\,Ha + 0.705\,Hd \quad \text{(Equation 3.13)}$$

N = 18, R^2 = 0.71, S = 1.04

$$\text{Log } K_p \text{ (cmh}^{-1}\text{)} = -2.65 - 0.0003\,MW - 0.0316\,SP - 0.0915 \log P + 0.332\,Ha - 0.418\,Hd \quad \text{(Equation 3.14)}$$

N = 18, R^2 = 0.30, S = 1.03

$$\text{Log } K_p \text{ (cmh}^{-1}\text{)} = -2.08 - 0.0029\,MW - 0.0352\,SP + 0.042 \log P - 0.02\,Ha + 0.207\,Hd \quad \text{(Equation 3.15)}$$

N = 18, R^2 = 0.41, S = 0.91

Group F (Section 2.4.8, Appendix 10) consists of compounds that exist both in the rodent as well as in the human skin dataset. Each compound has an assigned log K_p value. By linearly applying the regression analysis method to Group F compounds (Table 2.3), a prediction model was developed that was able to predict human permeability coefficient values derived from rodent permeability data. The resulting QSPR is described below in Equation 3.16.

$$\text{Log } K_p \text{ (human)} = 0.6502 \log K_p \text{ (rodent)} - 1.7062 \quad \text{(Equation 3.16)}$$

N = 54, R^2 = 0.27

It is apparent that the statistical fit of the data to the proposed model is poor. By obtaining a regression coefficient of 27% the model explains 27% variation within the data. The poor correlation with linearity might be in part again attributable to the dataset containing a diverse group of compounds in terms of chemical properties. In addition, the dataset included K_p values that were derived from multiple experiments. As already discussed in both Chapters 1 and 2, there is a great number of rodent *in vitro* experiments available in the literature. The resulting rodent K_p values could be used in the prediction of the corresponding human K_p

values. The constant of -1.7062 is used to correct the rodent K_p values in order to determine the corresponding human log K_p values.

Many coefficients existing in the Equations 3.2 - 3.16 have been shown to be extremely small. The variation in terms and magnitude is difficult to interpret. The magnitude in each term does vary extensively; as a result, its significance in equations becomes difficult to assess. Specifically, MW values are in the range of hundreds and theoretically have higher significance, whereas log P values range from below 1 to 5 and hydrogen bond acceptors and donors range from 1 to 6, thus theoretically having less significance. Therefore, due to the relative significance of these descriptors, it is difficult to assess the significance each descriptor has in the equation. Each coefficient does not explain the total effect on K_p of its corresponding variable as it would if it were the only variable in the model. Rather, it represents the additional effect of adding this variable to the equation, if the effects of all other variables are already accounted for. To avoid colinearity and effectively to avoid contributing the same information twice, there should be a balance between physicochemical parameters and the number of compounds involved. All the above equations are derived from datasets which are currently very small as far as the number of compounds is concerned. Therefore, over-representing of the data is to be expected in such linear relationships.

3.4.3.3. Data Manipulation on Different Ranges of Lipophilicity

Apart from analysing groups of data derived from different experimental conditions, it was considered of great importance to examine the effect of lipophilicity on skin penetration. The human skin log P values were divided into three distinct sets of 12 compounds each; the 'low log P value' category (log P < 1) – Group A22 (Appendix 5), the 'medium log P value' category (1 < log P < 3) – Group A23 (Appendix 5) – and the 'high log P value' category (log P > 3) – Group A24 (Appendix 5). The highest regression coefficient value set, indicating statistical superiority, was obtained from the model developed using the medium log P values (R^2 = 0.925, n = 12). These 12 compounds correspond to 12 different K_p values having been derived from 12 different log P values.

3.5. CONCLUSION

The majority of the QSPRs for skin permeability available in the literatureare are derived from uncertain sources, as already discussed in Chapter 2. In most cases, these data were not derived under carefully-controlled experimental conditions and sometimes were even computationally developed. The evaluation of current models with the use of more carefully-controlled experimental data was performed twice using two different Databases (B and C), resulting in poor correlations between the predicted and the experimentally-derived values of the permeation coefficients. This implied that the original data upon which the current QSPRs were developed accomodated the deficiencies in the experimental procedures well. Such models also do not adequately predict the K_p values of compounds with physicochemical properties outside the ranges of those of the original compounds used to develop them in the first place. Therefore, it is necessary that new

models are developed. By manually manipulating the datasets derived from different experimental conditions, novel linear QSPRs were developed. Even though these originated from better defined data, they were shown to have lower correlation coefficients. This was mainly due to the fact that, by classifying compounds into specific subsets, a smaller number of compounds with high diversity in terms of structure was used for their development (Table 3.10).

Finally and most importantly, it is the first time that the effects of ionisation have been taken into account and the pH in terms of log D has been incorporated into the permeability coefficient prediction. However, the main disadvantage of the linear models that dominate the literature to this date is that they assume linearity between the descriptors and skin permeability, suggesting that compounds of high lipophilicity / hydrophobicity cannot be accurately predicted. As a result, it was advocated that a new, non-linear model should be developed to tackle this problem and this approach is be discussed in Chapter 4.

Chapter Four

The Application of Data Mining Techniques in the Prediction of Skin Penetration

4.1. BACKGROUND AND RATIONALE

Predicting percutaneous absorption accurately has proven to be a major challenge with substantial implications for the pharmaceutical and cosmetic industries and for toxicological issues in fields such as the use of pesticides. Several approaches have been used to try to quantify and predict skin absorption. As discussed previously (Section 1. 8), one such method involves the use of QSPRs. Most QSPR models for skin permeability have employed the multi linear regression (MLR) method. The method provides an efficient way to determine the most relevant physicochemical descriptors but, as discussed in Chapter 3, the main disadvantage of the MLR approach is that it assumes linearity between the descriptors and skin permeability. Recently, newer approaches, such as the use of Artificial Neural Networks (ANNs, Section 1.8.2.4.2) and Fuzzy Modelling (Section 1.8.2.4.4), have been applied to this problematic domain, with varying degrees of success (Degim et al. 2002). The ANN method is much more computationally intensive than linear regression since the nonlinear regression coefficients (weights and biases) must be changed iteratively, which requires repeated evaluation of the network outputs (Atanasov 2006). Also, ANN is more complicated in terms of interpretation. Nevertheless, it has been considered as more suitable for extracting both linear and non-linear effects of chosen descriptors on skin permeability.

Fuzzy logic is a powerful tool that has been successfully used for modelling, control systems, pattern recognition, image processing and detection of distorted plethysmogram pulses (Tizhoosh 2000; Babuška 1998). With respect to fuzzy models, the criteria for a 'good' model are that its outputs should closely correlate to experimental outputs (reflected in a correlation coefficient), that it uses few inputs, that it enhances understanding of the phenomenon and that it is easy to use (Pannier et al. 2003). Future works should include attempts to study and extract information from the models and cluster structures within, to gain a better understanding of the essential components of skin permeability. Additionally, future models should attempt to capitalise on the ability of fuzzy modelling to integrate expert opinion and conditional parameters. With larger datasets, more sophisticated clustering techniques and expert insight into the data structure, fuzzy logic could be a very good approach to modelling skin permeability, along with other parameters in medicine (Pannier et al. 2003).

As already analysed in the previous chapters, Potts and Guy (1992) used the Flynn dataset to derive a linear equation that quantified percutaneous absorption. This model, as described in Section 1.8.2.2.1, has been continuously validated and modified in the intervening years and several similar equations have been developed since. Many researchers have demonstrated that certain data, especially compounds with high log P values, often have to be eliminated unjustifiably from the datasets because their behaviour does not comply with a standard model (Moss & Cronin 2002; Fitzpatrick et al. 2004). Interestingly, Moss et al. (2002) showed that the greatest difference between experimental and predicted permeability coefficient values was found at high log P values. If the absorption is ranked in terms of lipophilicity, it has been shown to have a Gaussian distribution (Sun et al. 2008). This phenomenon contradicts the linear nature of the Potts and Guy (1992) and any similar equation already developed. As such, one of the main objectives of this Chapter was to investigate the linearity or otherwise of the datasets employed for skin absorption.

4.1.1. The Data Used for QSPRs Predictions

The development of QSPRs for any endpoint requires some biological factor to model and without such data, no modelling is possible. The limitations of the data to be modelled (both biological and physicochemical) must be appreciated by both the model developer and the user. As already discussed in Chapter 3, the quality of the predictions of the developed permeation model depends on the consistency and quality of the experimental data used. The permeation data employed in modelling are mostly centred on the Flynn dataset with the addition of more recent data. During modelling efforts, outliers were discovered and this instigated rigorous examination of the reliability of data both in the Flynn dataset and other more recent datasets. For example, Degim et al. (1998) found anomalous results for naproxen, atropine and nicotine in the Flynn dataset and new values for these compounds were determined alongside values for aspirin, benzoic acid, diclofenac, ibuprofen and methyl nicotinate. Furthermore, according to Vecchia and Bunge (2003), the values for ethyl benzene, styrene and toluene should not be used. To avoid any variation in the data, well-constructed datasets must always be employed (Sun et al. 2008), as described earlier in Chapter 2, by screening compounds according to specific acceptance criteria.

4.1.2. Statistical Techniques

A statistical technique, as discussed in Section 1.8.3, is required to create some form of algorithm for various purposes, ranging from regression analysis through to more multivariate approaches, such as partial least squares, principal component analysis or the use of artificial neural networks. It has been accepted that it is best to employ the simplest statistical approach possible (Cronin & Schultz 2003). According to these latter workers, regression analysis is the statistical method of choice, being simple, easy to interpret and highly portable. On the other hand, the degree of statistical fit should also be considered since there is no point in using simple statistical means at the expense of losing statistical fit. The key issue is to find and employ a method that provides the greatest statistical fit, irrespective of its nature. As already discussed earlier, the use of linear models to represent skin permeability might not provide the most accurate of predictive models with the general approach of such models limiting the range to molecules with log P values smaller than 3.

The use of such models in this manner is inappropriate, as it does not fully reflect the spread of the dataset. The treatment of outliers has sparked controversy among QSPR developers for decades (see examples in Moss et al. 2002; Cronin 2006; Fitzpatrick et al. 2004). As indicated previously (Section 3.1.2), the most simplistic approach is to remove outliers and then assume they do not exist. However, the removal of outliers should only be performed on a rational basis according to clearly defined reasons, such as compounds acting by a different mechanism or as a consequence of them being poor quality data (e.g. derived using inappropriate methods), and not merely because they decrease the model's statistical robustness. There is therefore compelling qualitative evidence suggesting that the non-linear response to skin absorption observed experimentally is not accomodated by linear modeling and thus, the data should be modelled using alternative mathematical techniques. The use of linear approaches can lead to loss of critical information and the resultant models may have poor predictive abilities (Golla et al. 2009).

4.1.3. The Theoretical Backgrounds of the Mathematical Models

4.1.3.1. QSPRs Analysis

Diverse statistical methods have been applied to the building of QSPRs, some linear in their nature and others nonlinear (Livingstone 1995). A great number of linear QSPRs have been applied extensively and successfully over several decades to find predictive models for the activity of bioactive agents. It has also been applied to areas related to discovery and the subsequent development of bioactive agents distinguishing drug-like from non-drug-like molecules, drug resistance, toxicity, prediction, gastrointestinal absorption activity of peptides, data mining, drug metabolism and prediction of absorption distribution metabolism and elimination (ADME) properties. The application of nonlinear methods, such as ANNs, to the majority of these areas has demonstrated superiority over the linear algorithms in terms of statistical fit and provided a better predictive profile (Winkler 2002). Specifically, nonlinear QSPR models for the prediction of refractive indices of polymers have been developed in addition to linear models, based on a diverse dataset comprising 120 polymers, by using both multilinear regression analysis and feed-forward artificial neural networks; it has been shown that better results were obtained from the nonlinear models (Xu et al. 2008). Furthermore, with respect to assessing toxicity, QSARs were derived from a structurally heterogeneous set of 200 phenol derivatives for which the 50% growth inhibition concentration (IGC50) values to the ciliated protozoan Tetrahymena pyriformis were available. Each molecule was described by means of physicochemical descriptors and structural features. The performances of the linear and nonlinear models were estimated from an external testing set of 50 chemicals. Despite hard constraints voluntarily imposed in the design of the neural network models, they provided better simulation results than those obtained using the previously reported linear models (Devillers 2004).

Similarly, a great number of linear and nonlinear algorithms have been developed to predict skin permeability coefficients. Recently, the mathematical methods used as linear regression tools in QSPR analysis have been developing quickly and along with the use of nonlinear models such as ANNs and Fuzzy Logic (Liu & Long 2009). Additionally, in Chapter 3, it was shown that there were significant differences between the experimentally derived log K_p values and those that were predicted via a series of linear models, especially for the compounds of high log P values. This was also verified by literature findings according to which compounds with low hydrophilicity and hence high log P values permeate slowly or are poorly absorbed (Potts and Guy 1992; Funke et al. 2002). In effect, the absorption is Gaussian in its distribution, particularly if assessed by log P. This contradicts the linear nature of the Potts and Guy (1992) (and similar) equations, although the concomitant increase in log P and MW is often offset by the negative sign in front of MW. Nonlinear modelling might therefore provide a better prediction of the percutaneous absorption of molecules with a wide range of log P values.

4.1.3.2. Single Layer Artificial Neural Network

Regression analysis was initially carried out on the human skin dataset (Group A18) using a single layer network (SLN). The most basic kind of neural network is a single-layer network, which consists of a single layer of output nodes; the inputs are fed directly to the outputs via a series of connection weights vectors. An important component of most neural networks is the learning rule. The learning rule allows the network to

adjust its connection weights in order to associate given input vectors with corresponding output vectors. During training periods, the input vectors are repeatedly presented and the weights are adjusted according to the learning rule, until the network learns the desired associations.

4.1.3.3. Gaussian Process (GP) Regression

Gaussian process (GP) is defined simply as a collection of random variables, which have a joint Gaussian distribution. Whereas a probability distribution describes random variables which are scalars or vectors (for multivariate distributions), a stochastic process governs the properties of functions. Leaving mathematical sophistication aside, it is possible to loosely think of a function as a very long vector, each entry in the vector specifying the function value f(x) at a particular input x.

GP modelling is a non-parametric method. It does not produce an explicit functional representation of the data, as QSPR modelling does in the form of an equation, where the permeability is usually related to statistically significant physicochemical descriptors of a dataset. In GP modelling it is assumed that the underlying function, *f*(x), that produces the data will remain unknown, but that the data are produced from a(n) (infinite) set of functions, with a Gaussian distribution in the function space. From a slightly different viewpoint, it is clear that in supervised learning the notion of similarity between data points is crucial. It is a basic similarity assumption that considers inputs, x, which are likely to have similar values to target outputs, y, and, thus, training points that are near to a test point should be informative about the prediction at that point. Under the Gaussian process, it is the covariance function that defines nearness or similarity (Rasmussen & Williams 2006). The latter workers have provided a comprehensive review of Gaussian processes to which the reader is directed for a more in-depth discussion on the background to this subject. However, GPs suffer from one important limitation in that they are computationally impractical for large datasets (Rasmussen & Ghahramani 2001).

4.1.3.4. K-Nearest-Neighbour (KNN) Regression

One of the most important concerns in high-dimensional problems is to take into account the local structure of the data and it appears that a well adapted tool is the K-Nearest-Neighbour (KNN) method (Burba et al. 2009). In pattern recognition, the KNN algorithm is a non-parametric method for classifying objects based on closest training examples in the feature space. KNN is a type of instance-based learning, or lazy learning, where the function is only approximated locally and all computation is deferred until classification. The KNN algorithm is amongst the simplest of all machine learning algorithms. It can be used for classification purposes or as a regression tool, by simply assigning the property value for the object to be the average of the values of its K nearest neighbours. Given a test input vector x, the algorithm finds the K closest points to x among all the training inputs. The prediction of the model is therefore the average of those K target values. There are several serious disadvantages to the use of the nearest-neighbour methods. First, they do not simplify the distribution of objects in parameter space to a comprehensible set of parameters. Instead, the training set is retained in its entirety as a description of the object distribution. The method is also rather slow if the training set has many examples.

4.1.3.5. Mixture-of-Experts (ME)

The mixture-of-experts (ME) architecture is a model in which the mixture components are conditional probability distributions. ME architectures are generally used for regression or classification problems (Jacobs 2008). They are interesting because they attempt to decompose complex problems into a set of simpler subproblems. The data can be adequately summarised by a collection of functions, each of which is defined over a local region of the domain. The approach adopted here attempts to allocate different modules (experts) to summarise the data located in different regions. The gating network receives the input x and outputs a scalar value p_i with the property that $p_i \geq 0$ and $\Sigma_i p_i = 1$. The final prediction of the model is a sum of the expert predictions weighted by p_i. In this work, all local experts used to analyse the data in each region are linear regression models.

4.1.3.6. Multivariate Data Analysis Techniques

Multivariate data analysis techniques have been used for analysing voluminous environmental data (e.g. Buhr et al. 1992; Schuag et al. 1990; Ziomas et al. 1995). There are many different models, each with its own type of analysis. Examples of multivariate data analysis techniques include Canonical Correlation (CC) as well as Principle Component Analysis (PCA), both of these methods being conceptually similar. Canonical correlation is one of the most general of the multivariate techniques, which is used to investigate the overall correlation between two sets of variables. The basic principle behind this approach is determining how the degree of variance in one set of variables is accounted for by the variance in the other set along one or more axes. Unlike many other techniques, there is no designation that one set of variables is independent and the other set dependent. Canonical correlation provides a convenient way to understand the complex relationships that might exist between the variables. PCA is a type of factor analysis that is most often used as an exploratory tool. It is used to simplify the description of a set of many related variables; PCA reduces the number of variables by finding new components that are combinations of the old variables. Usually, most of the variation in a large group of variables can be captured with only a few principal components. PCA can also be useful as a preliminary step in a complicated regression analysis as well as other statistical tests. Whereas PCA attempts to explain the linear relationship among a set of observed variables and an unknown number of variates, CC focuses more on the linear relationship between two variates.

4.2. AIMS AND OBJECTIVES

The aim of the current study was to demonstrate the feasibility of prediction improvement by using advanced computational regression modelling methods. The main objective was therefore to introduce advanced machine learning techniques, such as Gaussian processing, a method that has never been applied in the past to skin permeability data. The secondary objective was to investigate the advisability of including additional descriptors into the equation under development.

4.3. METHODS

In this work, a SLN ANN model and a GP model were both developed by using regression computation statistical methods with a view to predicting the skin permeability coefficient of penetrants. Additionally, for comparison

purposes, the Potts and Guy (1992) together with the Moss and Cronin (2002) models were employed to determine relevant permeability coefficient of the penetrants. Finally, a ME and a KNN regression model were also developed and applied. Two different skin datasets were used, one comprising 142 compounds (Group A18) and another comprising 149 compounds (Group A19). The difference between these two datasets is described in detail in Section 4.3.1.

4.3.1. Description of the Data

Due to the limited size of the 'ideal' dataset in terms of the number of K_p values that have been generated under specified tightly controlled conditions, as described previously in Section 2.4.3.1, the models under investigation were applied to two large datasets. The first dataset, employed in this chapter, consisted of human data alone (Database C, Appendix 5, Group A18), whereas the second dataset consisted of both human and pig skin data (Database C, Appendix 5, Group A19). The pig skin data were also incorporated with the first (human) dataset because the pig stratum corneum has been reported previously to be the most similar to human stratum corneum in terms of lipid composition (Cilurzo et al. 2007; Simon et al. 2000). Improved K_p models using a combination of predictive descriptors and statistically determined descriptors were established and all models were developed based on both datasets. Specifically, the first dataset under investigation was initially described in Section 2.4.3.13, as Group A18 (142 compounds). Group A18 consisted of 37 chemicals retrieved from the Flynn dataset, several others from Patel et al. (2002a) as well as further molecules from the EDETOX database. Also, borax, erioglaucine and epikote XY4000 were eliminated due to the fact that some of their descriptors could not be defined (e.g. SP, MPt, Ha, etc.). Each compound in the dataset was defined by six molecular descriptors and experimental values for K_p for permeation across human skin only. The physicochemical parameters employed were molecular weight (MW) and log P for the 2f models. Molecular weight (MW), log P, Fedors' solubility (SP), hydrogen bond donor (Hd) and hydrogen bond acceptor (Ha) were used in the development of the 5f models. Finally, molecular weight (MW), log P, Fedors' solubility (SP), hydrogen bond donor (Hd), hydrogen bond acceptor (Ha) and melting point (MPt) were utilised to generate the 6f models. The usefulness of melting point as a descriptor has never been addressed fully, although Barratt et al. (1995) proposed that it could be combined with log P_{ow}, as a measure of aqueous solubility. However, there were difficulties in calculating the exact melting point of the compounds (usually a MPt range is quoted in the literature). Consequently, melting point was not included in the second assembled dataset (Appendix 5, Group A19).

The selection of possible descriptors was based on past literature, specifically the effect of lipophilicity, hydrogen bonding, molecular weight and molecular point were considered highly significant in their influence and thus in predicting prermeability (Michaels et al. 1975; Lam et al. 2010). Furthermore, the effect of Fedors' solubility upon permeability was investigated by Moss et al. 2009 and Moss et al. 2011. Fedors' solubility is an important predictor as it relates the solubility of a penetrant to the solubility of the stratum corneum, the skin barrier. Feature selection to determine key physiochemical description, which would exert most significant influence on percutaneous absorption, was not conducted in the context of this thesis. However, conclusions were drawn from the analysis performed by Lam et al. 2010; it was shown that significant synergy existed between certain parameters and as such, it was possible to interchange certain descriptors, i.e. molecular weight and melting point, without incurring a loss of data quality.

Depending on the nature of the data, different parameters can offer different degrees of descriptor dependability in percutaneous absorption (Potts & Guy 1992; Lam et al. 2010).

The second dataset, employed in this chapter, Group A19 (Appendix 5, Group A19) was described in Section 2.4.3.14 and was collated with reference to a range of literature sources. It consisted of the above-mentioned 142 compounds plus some additional molecules reported by Moss et al. (2006). These latter additional seven compounds were inserted into the second dataset in order to increase the statistical validity of the model. As a result, a whole dataset of 149 compounds (Group A19) was used in the relevant analyses. For both datasets, log P values were employed instead of log D values. As already discussed in Section 1.4.2.2, if a molecule exists in an ionisable form, then the pH of the aqueous phase will influence the concentrations of the ionised and neutral forms of the molecule and log D should be used instead to reflect the pH dependent lipophilicity of a drug (Dearden et al. 2009). In Chapter 3, it is clearly seen that for the modelling of skin penetration, it is usually considered preferable to use log D value instead of log P in order to account the ionisation effect. Nevertheless, due to the fact that the new linear models developed as described in Chapter 3 were concurrently generated alongside the nonlinear models constructed herein, the log D values for the 142 compounds (Group A18) and 149 compounds (Group A19) used for the GP model development had not been determined by that time. As a result, log P values were used instead.

4.3.2. Gaussian Process (GP) Regression

For Gaussian Process models, the Rasmussen and William's GP toolbox was applied to the data (Rasmussen & Williams 2006). The toolbox was implemented in MatLab (version 7.6, www.mathworks.com), a high level computing language used for algorithm development, numeric computation, data visualisation and analysis. The data were produced from a (infinite) set of functions, with a Gaussian distribution in the function space. A Gaussian process is a non-parametric stochastic process and was characterised by its mean, $E\,[\,f\,(\,x\,)\,]$, and covariance function, $k(x_i; x_j)$.

In this work, the squared exponential covariance function was applied, which incorporated noise into the model and has the following form (Equation 4.1):

$$k(X_i, X_j) = \sigma_f^2 \exp(-\frac{1}{2}(X_i - X_j)^T M (X_i - X_j)) + \sigma_n^2 \delta_{ij} \qquad \text{(Equation 4.1)}$$

where $M = l^{-2} I$, l is a vector of positive values, l is characteristic length-scale, σ_f is signal variance, σ_n is noise variance and δ_{ij} is the Kronecker delta which is one if $i = j$ and zero otherwise.

The mean prediction given by Equation 4.2 was employed in order to make a prediction for $f(\mathbf{x}_*)$ at a new input $\mathbf{x}_*$:

$$E[f_*] = \mathbf{k}_*^T (\mathbf{K} + \sigma_n^2 \mathbf{I})^{-1} \mathbf{y} \qquad \text{(Equation 4.2)}$$

where $\mathbf{k}_*$ denotes the vector of covariances between the test point and the N_{trn} training data; $\mathbf{K}$ denotes the covariance matrix of the training data; σ_n^2 denotes the variance of an independent

identically distributed Gaussian noise (which means observations are noisy); and $\mathbf{y}$ denotes the vector of training targets.

The variance at $\mathbf{x}_*$ is given by $var[f_*] = k(\mathbf{x}_*, \mathbf{x}_*) - \mathbf{k}_*^T(\mathbf{K} + \sigma_n^2\mathbf{I})^{-1}\mathbf{k}_*$, where $k(\mathbf{x}_*, \mathbf{x}_*)$ denotes the variance of f_*.

4.3.3. Single Layer Network (SLN), K-Nearest-Neighbour (KNN) and Mixture-of-Experts (ME)

The Netlab Toolbox was used for single layer network (SLN) and was also implemented at MatLab (version 7.6, www.mathworks.com). The regression analysis method was carried out on the skin dataset using SLN. The output y was determined, as the weighted sum of the components of an input vector x (Equation 4.3):

$$y = y(x; w) = \sum_{i=1}^{d} w_i x_i + w_o \qquad \text{(Equation 4.3)}$$

where d was dimensionality of the input space and w = (w_1,……w_d, w_o) the weight vector. The weights were set so that the sum squared error function was minimised using a training set of compounds. The Euclidean distance was applied to the KNN regression and the ME model was developed via linear regression.

4.3.4. Multivariate Data Analysis Techniques

For Group A18 (142 compounds), PCA, as described earlier, was used to find a projection that maximised the correlation between two sets of variables. Molecular weight, Fedors' solubility, log P, hydrogen bond donor and acceptor and melting point were grouped into one set and log K_p into another set, in order to investigate the correlating linear relationship between log K_p and the six compound descriptors. The first principal component, PCA1, was identified as the vector, or equivalently the linear combination of variables, on which the most data variation can be projected. A linear line going through the mean of the multivariate dataset, was developed (Equation 4.4) and the square of the distance of each point to that line was minimised. The coefficients of the principal components were calculated so that the PCA1 contained the maximum variance. The second PCA axis went through the mean of the multivariate dataset and also through the maximum variation in the data, but with a certain constraint. PCA axis 2 was completely uncorrelated in a linear sense to PCA axis 1. Both PCA 1 and PCA 2 equations are shown in detail in the results section of this chapter.

For Group A19 (149 compounds), the canonical correlation was used. Molecular weight, Fedors' solubility, log P, hydrogen bond donor and acceptor were grouped into one set and log K_p into another set, in order to investigate the correlating linear relationship between log K_p and the five compound descriptors.

4.3.5. Performance Measures

For assessing regression performance, four common measurements were applied to both datasets (Group A18 and Group A19). These measurements consisted of the normalised mean squared error (NMSE), negative log loss (NLL), the correlation coefficient (CORR) and the percentage improvement over a naïve model (ION).

4.3.5.1. Mean Squared Error (MSE)

The Mean Squared Error (MSE) of an estimator measures the average squared difference between model predictions and the corresponding targets. For the purpose of performance measurement NMSE was reported. NMSE is the normalised MSE which is obtained by accommodating the variance of the target values, i.e. by taking into account the range of observed values.

$$\mathrm{NMSE} = \frac{1}{N_{tst}} \sum_{n=1}^{N_{tst}} \frac{(y_n^{tst} - \hat{y}_n)^2}{var(y)}. \qquad \text{(Equation 4.4)}$$

where N_{tst} is the test input - target pairs, $\hat{y}_n$ is model prediction and y_n^{tst} is the test targets.

4.3.5.2. Percentage Improvement over a Naïve Model (ION)

In the naïve model for any input the prediction is always the same value, namely the mean of log K_p in the training set, defined by Equation 4.5:

$$\hat{y}_{naive} = \frac{1}{N_{trn}} \sum_{n=1}^{N_{trn}} y_n^{trn} . \qquad \text{(Equation 4.5)}$$

Thus, the mean squared error of a naïve model was calculated by Equation 4.6:

$$MSE_{naive} = \frac{1}{N_t st} \sum_{n=1}^{N_{tst}} (\hat{y}_{naive} - y_n^{tst})^2 . \qquad \text{(Equation 4.6)}$$

The degree of improvement of the model over the naïve predictor was quantified by the improvement over naïve (ION) measure (Equation 4.7):

$$ION = \frac{MSE_{naive} - MSE}{MSE_{naive}} \times 100\% \qquad \text{(Equation 4.7)}$$

4.3.5.3. Negative Log Loss (NLL)

When determining the statistical fit to the GPP mode, the average negative log loss (NLL) needed to be considered and was given by Equation 4.8:

$$NLL = \frac{1}{n}\sum_{n=1}^{Ntst} -\log p(y_n \mid x_n) \qquad \text{(Equation 4.8)}$$

where

$$-\log p\,(y_n / x_n) = \tfrac{1}{2}\log(2\pi\sigma^2_*) + (t_* - E\{f_*\})^2 / 2\,\sigma^2_* \qquad \text{(Equation 4.9)}$$

where σ^2_* is the predictive variance.

The NLL measure was used for both basis vector selection and hyper parameter adaptation.

4.3.6. Training Procedure

The split sample approach is a widely used study design in high dimensional settings (Dobbin et al. 2011). This design divides the collection into a training set and a test set as a means of estimating classification accuracy. A more sophisticated approach is to use cross validation, which can be seen as an extension of the split-sample method. With split-half cross-validation, the model is developed on one randomly drawn half and tested on the other, and vice versa (Efron & Tibshirani 1993). The k-fold cross-validation data are split into k subsamples, equally sized subsets; validation is done on a single subset and training is done using the union of the remaining k^{-1} subsets, the entire procedure being repeated k times, each time with a different subset for validation.

However, due to the small size of the datasets, cross validation was not employed as a splitting approach. Rather, a 10-fold validation was used instead, giving the advantage that the proportion of the training / validation split was not dependent on the number of iterations (folds). The experiment was repeated 10 times and generated 10 different training sets. Dealing with small datasets creates particular problems, as test sets may be very small. For the purpose of this training, 12 (or 19) points were randomly selected each time. The training procedure of the Group A18 (142 compounds) involved the whole dataset being randomly divided into a training set and an independent test set. The training set consisted of 130 compounds, while the test set consisted of the remaining 12. Additionally, the training procedure of the Group A19 (149 compounds) involved the whole dataset being split into 130 compounds in the training set and the remaining 19 into the validation set. The split of compounds between the training set and the test set was performed on the basis repeated random sampling validation. The best splitting strategies would be to use one third of the data into the test set and the remaining two thirds in the training set (Dobbin et al.

2011). However, the problem with the dataset was that it was rather small and therefore a smaller test set was preferred. Consequently, approximately 90% of the data were used in the training set and the remaining 10% in the test set. Specifically, in Group A18, 91.5% of the data were used in the training set whereas in Group A19, 87.25% was used instead.

Initially, two regression methods were applied (SLN and GP) using two molecular descriptors, log P and MW. Models were evolved by integrating six parameters such as MW, MPt, SP, log P, Ha and Hd. A GP regression function (gpr.m) was employed, with a covariance function (the latter being the sum of squared exponential process and an independent noise process). The log of the hyperparameters was initialised with the logarithm of characteristic length-scale set to 0, the logarithm of signal variance to 1.0 and noise variance to 0.1. Next, the negative log marginal was minimised with respect to the log of the hyperparameters by using the function minimiz.m. When training compounds were included in the arguments to the gpr.m function they returned predictive mean values and variances as outputs.

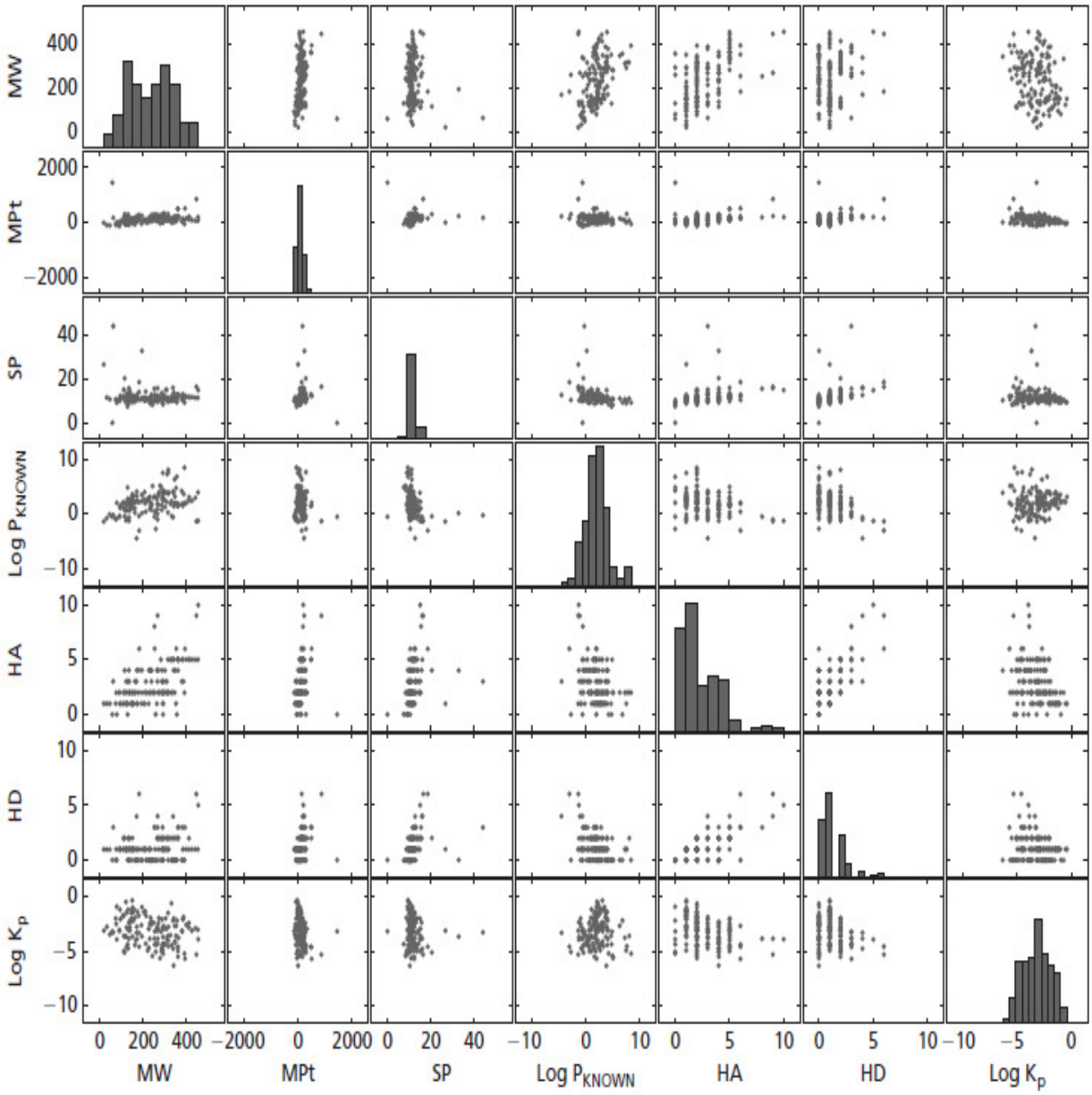
To further investigate the importance of including more than two molecular descriptors (two such features were used in the QSPR forms, i.e. MW and log P), regression-modelling methods with both two and five compound features as an input vector were employed. In KNN modelling, the number of neighbours was varied, K, between 1 and 10; in the ME, the number of experts was set between 2 and 5.

In GP modelling, the initial values of the logarithm of characteristic length-scale, the logarithm of signal variance and noise variance using cross validation were chosen from 10 user-defined pre-sets. For the purpose of this analysis, a five-fold cross-validation procedure was used in order to select optimal parameters for each of KNN, ME and GP. In these cases, each training set (130 compounds) was further divided into training and validation sets in order to find the most suitable parameters of the above-mentioned models.

4.4. Results and Discussion

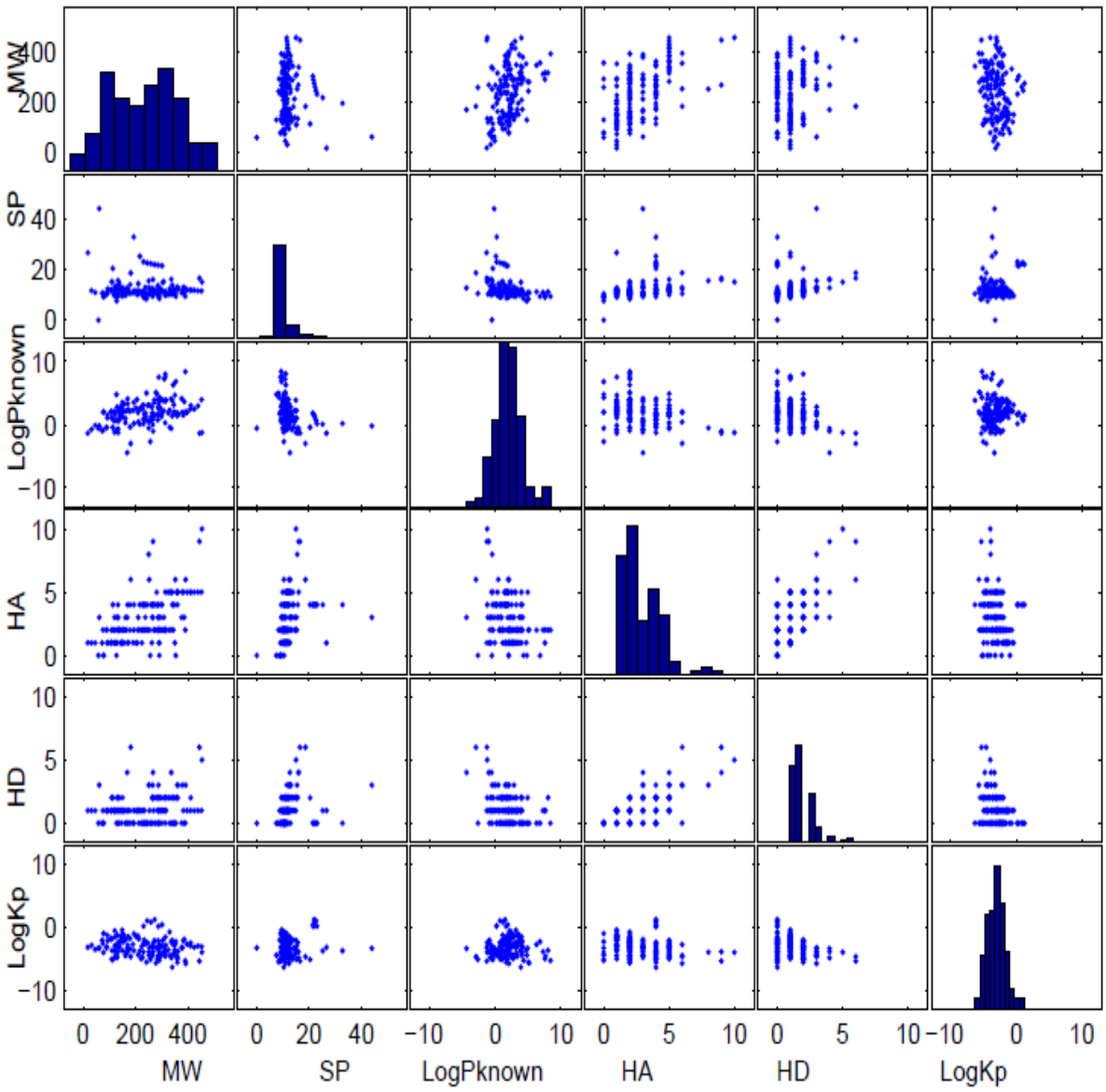
4.4.1. Visualisation of the Data

A scatter plot matrix of data for the 142 compounds (Group A18) was generated by plotting log K_p as a function of six selected molecular descriptors and as a function of each of the other (Figure 4.1). It was shown that there was no simple linear relationship between any pairs of descriptors. The same trend was observed when a scatter plot matrix of data for all 149 compounds (Group A19) with log K_p was plotted as a function of five selected molecular descriptors and as a function of each of the other (Figure 4.2). The diagonal insets (Figures 4.1 and 4.2) are different in that they show the shape of the distribution of each feature. The subplots appearing in the first rows and last columns show MW against log K_p. They suggest that very similar values of log K_p can correspond to many different MW values. The same occurred when log P was plotted against log K_p also when SP was plotted as a function of log K_p and indeed there appears to be no simple linear relationship between any set of descriptors.



	MW	MPt	SP	Log P	Ha	Hd	Log K_p
MW	1.0000	0.2570	-0.1240	0.3892	0.5580	0.1941	-0.2767
MPt	0.2570	1.0000	0.0202	-0.1289	0.3026	0.3197	-0.2740
SP	-0.1240	0.0202	1.0000	-0.3078	0.2604	0.3521	-0.1012
Log P	0.3892	-0.1289	-0.3078	1.0000	-0.3093	-0.3897	0.0655
Ha	0.5580	0.3026	0.2604	-0.3093	1.0000	0.6327	-0.3709
Hd	0.1941	0.3197	0.3521	-0.3897	0.6327	1.0000	-0.2411
Log K_p	-0.2767	-0.2740	-0.1012	0.0655	-0.3709	-0.2411	1.0000

Figure 4.1. A scatter plot matrix of the skin Group A18 (n = 142) containing six molecular descriptors and log K_p.



	MW	SP	Log P	Ha	Hd	Log K_p
MW	1.0000	-0.1297	0.3911	0.5460	0.1726	-0.2693
SP	-0.1297	1.0000	-0.3320	0.2747	0.3734	-0.1300
Log P	0.3911	-0.3320	1.0000	-0.3263	-0.4227	0.1026
Ha	0.5460	0.2747	-0.3263	1.0000	0.6320	-0.3849
Hd	0.1726	0.3734	-0.4227	0.6320	1.0000	-0.2676
Log K_p	-0.2693	-0.1300	0.1026	-0.3849	-0.2676	1.0000

Figure 4.2. A scatter plot matrix of the skin Group A19 (n = 149) containing five molecular descriptors and log K_p.

4.4.2. Multivariate Data Analysis Techniques

The coefficients of the principal components were calculated so that the PCA 1 contained the maximum variance determined by the following Equation 4.10:

$$PCA1 = 0.272\,MW + 0.336\,MPt + 0.306\,SP - 0.313\log P + 0.567Ha + 0.548Hd \quad \text{(Equation 4.10)}$$

where MW, MPt, SP, log P, Ha and Hd are the normalised variables. All six features contributed to this component, as all coefficients are relatively large.

PCA2 was given by the following Equation 4.11.

$$PCA2 = -0.668MW - 0.201MPt + 0.396\,SP - 0.566\log P - 0.173Ha + 0.089Hd \quad \text{(Equation 4.11)}$$

The same results were obtained when the Classic Principal Component Analysis was used as an additional data analysis technique for both the 142 compound dataset (Group A18) as well as for the 149 compound dataset (Group A19). Classic PCA is a projection method in which a linear transformation is used to map data to a lower dimensional space. It is one of the most popular techniques for preprocessing and visualising high dimensional data. In practice, in order to map vectors xn in a D-dimensional space onto a lower d-dimensional space (where $d < D$), the data should be preprocessed so that the mean is zero. Next the covariance matrix of the data is computed and its principal components (PCs) are obtained as the eigenvectors of this matrix. The data are projected onto the first L principal components corresponding to the largest L variances in the new set of coordinates. For the purpose of this thesis, compounds were plotted using the corresponding log K_p values and the first two principal components for representing the variation in the molecular descriptors of the members of the dataset. This technique was initially used to visualise the data, in order to determine whether their underlying nature was linear or nonlinear. Before predicting the skin permeability coefficients, the underlying data distribution was investigated by means of data visualisation technology, which projects data into a low dimensional space. The dataset with the 149 compounds was initially visualised using PCA projections. All five features contribute to this component (all coefficients are relatively large). The first two principal components account for 73.1% of the total variance. Figure 4.3 clearly indicates that there is no linear relation between log K_p and the compound features.

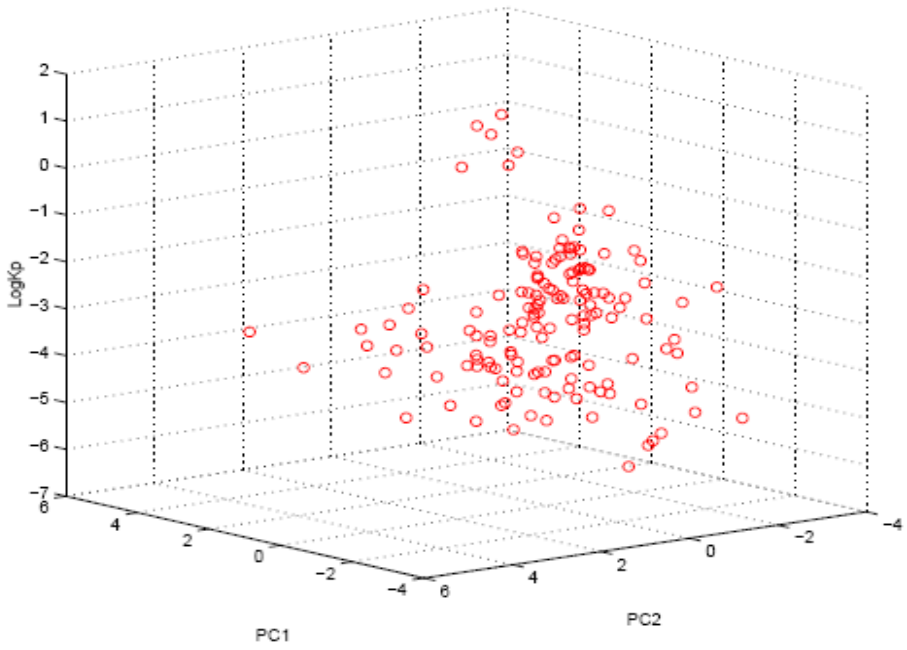


Figure 4.3. Initial analysis of Group A19 (n = 149) by principal component analysis showing log K_p against two principal components (five descriptors).

Similarly, with regards to the 142 compound dataset (Group A18), all six features contribute to this component (all coefficients are relatively large). The first two principal components together account for 66.2% of the total variance in the dataset. Figure 4.4 shows that there is no linear relation between log K_p and the compound features, suggesting that there may be more complex nonlinear structures in the data.

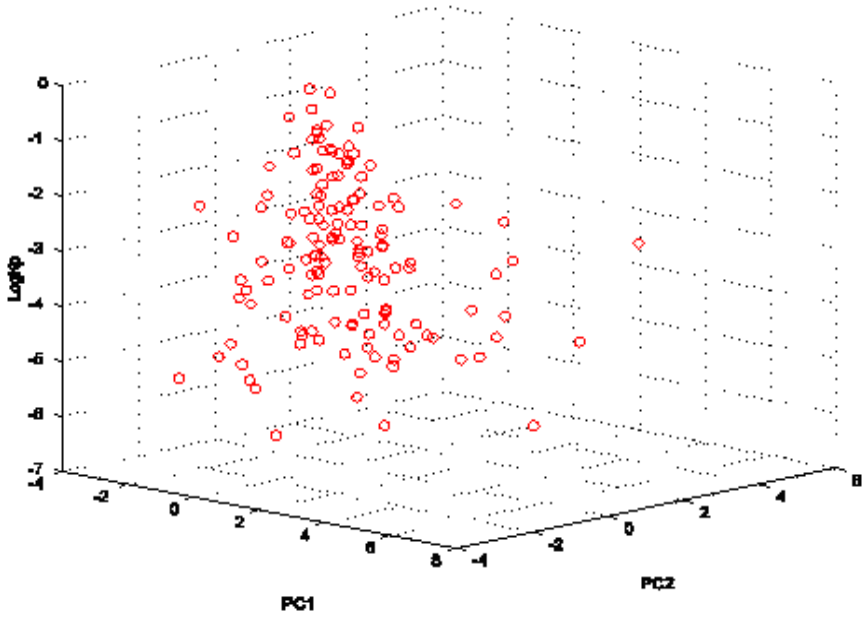


Figure 4.4. Initial analysis of Group A18 (142 compounds) by principal component analysis showing log K_p against two principal components (six descriptors).

Eigenvalues, otherwise known as the characteristic values, can be thought of as quantitative assessment of the impact a certain component has upon the data. The higher the eigenvalues of a component, the more representative it is of the data. Eigenvalues can also be representative of the level of explained variance as a percentage of total variance, but by themselves, such values are not completely informative. The percentage of explained of variance is dependent on the extent that the specific components summarise the data. In theory, the sum of all components explains 100% variability in the data (Jolliffe 2005). In both datasets, the sum of all components explained a less-than-100% variability in the data, indicating other factors such as nonlinearity exist within the data.

For Group A19 consisting of 149 compounds, the canonical correlation was used and CV 1 and CV 2 were obtained using Equations 4.12 and 4.13:

$$CV\ 1 = 0.002MW - 0.116SP + 0.033 \log P + 0.107Ha + 0.6655Hd \quad \text{(Equation 4.12)}$$

$$CV\ 2 = -0.686 \log K_p. \quad \text{(Equation 4.13)}$$

The canonical variable 1 (CV 1) is a combination of five descriptors, applied to Group A19 (149 compounds), as shown in Figure 4.5, while the canonical variable 2 (CV 2) is given by CV 2 = 0.686 log K_p. There is no linear relationship between the two sets of variables. It is interesting to note that in CV 1 the least important features (those with lowest coefficients) are MW and log P. The overall canonical correlation coefficient was approximately 0.415, whereas the canonical correlation coefficient between log K_p and a group of two variables, MW and log P was about 0.238.

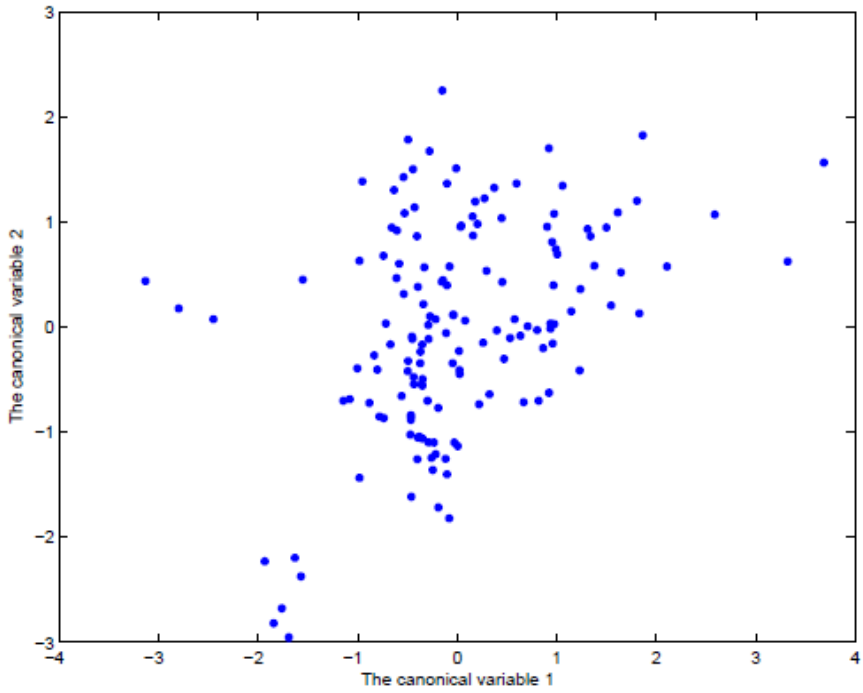


Figure 4.5. Canonical correlations between five compound descriptors and log K_p.

The use of both the above PCA and the CCA indicates that a nonlinear approach to predicting skin permeability is essential, given the inherent nature of the skin dataset being employed (Statheropoulos et al. 1998). As already discussed earlier in this section, PCA is mathematically defined as an orthogonal linear transformation that transforms the data to a new coordinate system such that the greatest variance by any projection of the data comes to lie on the first coordinate (called the first principal component), the second greatest variance on the second coordinate and so on. This transformation is defined in such a way that the first principal component has as high a variance as possible (that is, accounts for as much of the variability in the data as possible) and each succeeding component in turn has the highest variance possible under the constraint that it be orthogonal to (uncorrelated with) the preceding components (Shaw 2003). Consequently, by not obtaining a high total variance in the dataset, this implies the presence of nonlinearity within the data.

All results obtained from both established QSPRs as well as from trainable regression analyses using both Groups A18 and A19 are summarised in Tables 4.1 and 4.2. The regression coefficient values together with the corresponding NMSE, % ION and NLL values are summarised in Table 4.1. With regards to analysing the performance of the models in this study, the objective was to obtain a model, which for the test set would provide low values of both NMSE and NLL as well as high values of both ION and correlation coefficient (CORR) for a given test dataset.

Table 4.1 indicates that the naïve model, as defined in Section 4.3.5.2, was shown to have better predictivity than the QSPR model (Moss & Cronin 2002), in terms of having a higher % ION value and a smaller NMSE value. The Moss and Cronin (2002) model was not used in the re-evaluation process in Chapter 3; instead, the Potts and Guy (1992) model was preferred since it was the most-cited QSPR and used the same parameters with Moss and Cronin (2002) anyway. Nevertheless, the latter model, already analysed in detail at Section 1.8.2.4.3, is used as a reference model in Chapter 5, as being derived from Potts and Guy (1992). Furthermore, the naïve model showed that the trainable SLN model produced better predictivity when compared to that obtained from the Moss and Cronin (2002) model, due to the former model having a higher % ION and lower NMSE values. Also, the SLN 6f model was found to have a greater regression coefficient value when compared with the regression coefficient of the Potts and Guy (1992) model. Regression coefficients provide information about the goodness of fit of a model with the regression coefficient of determination being a statistical measure of how well the regression line approximates the real data points. A value of 1.0 indicates that the regression line perfectly fits the data. Consequently, higher regression values suggest a better prediction in terms of statistical fit (Cameron & Windmeijer 1997).

Additionally, the GP model provided better predictivity than the SLN model (Table 4.1). These results suggest that when a nonlinear model was employed, the predictions were significantly better than those obtained from the linear model. The inclusion of highly lipophilic and hydrophilic molecules in the dataset is better predicted by the use of nonlinear techniques, since linear methods, when incorporating such compounds, provide lower regression coefficient values indicating a lower statistical fit. The GP model encompassing six molecular features provides an even more accurate model (R^2 = 0.59) than the GP incorporating two features (R^2 = 0.53), suggesting that the addition of four more features improves the predictive capabilities of the GP regression model. The machine learning methods showed that models with six features had better predictivity

than those obtained using only two features, when considering NMSE, ION and regression coefficient values. This result shows that, by incorporating two inputs rather than six, a more robust model is obtained, leading to better permeability coefficient predictions. However, Table 4.1 demonstrates that both SLN and GP with either two or six features produce statistically more robust models than the Moss and Cronin (2002) model, since the latter shows significantly worse predictivity with a regression coefficient of 0.38. This is likely to be due to the fact that inferior quality data were used in the Moss and Cronin (2002) development rather than in the SLN and GP models, thus, producing an algorithm of worse statistical fit.

Finally, by comparing the Moss and Cronin (2002) regression coefficient, summarised in Table 4.1, with the one existing in literature (Section 1.8.2.4.3), it can be seen that a smaller regression coefficient is obtained by using the 142 compounds, demonstrating that the model available in the literature was developed for a specific set of compounds and the addition of more compounds (as employed here) determined its descriptive capacity.

Table 4.1. Normalised Mean Squared Error (NMSE), % improvement over the naïve model (ION %), R^2 and NLL measurements of a number of different models by using two and six physicochemical descriptors.

Models	NMSE	ION (%)	R^2	NLL
Naïve	1.16 ± 0.12	0	-	-
QSPR (Moss and Cronin 2002)	1.48 ± 0.23	-35.55 ± 21.15	0.38 ± 0.07	-
SLN 2f	1.02 ± 0.10	11.20 ± 5.00	0.38 ± 0.24	-
GP 2f	0.84 ± 0.09	25.48 ± 6.82	0.53 ± 0.07	1.60 ± 0.06
SLN 6f	1.00 ± 0.10	11.77 ± 6.30	0.43 ± 0.08	-
GP 6f	0.72 ± 0.10	35.51 ± 8.30	0.59 ± 0.08	1.61 ± 0.13

Moreover, the results in Table 4.2 show that the naïve model produced a better predictivity than the two analysed QSPR models which display values below zero in terms of % ION. Therefore, in general, the QSPR predictions proved to be less robust than naïve predictions, especially when the Potts and Guy (1992) model was compared with the naïve model. It should be noted that the SLN still produced a statistically more robust model than either Potts and Guy (1992) and Moss and Cronin (2002).

Table 4.2. Normalised Mean Squared Error (NMSE), % improvement over the naïve model (ION %), R^2 and NLL measurements of a number of different models by using two and five physicochemical descriptors.

Models	NMSE	ION (%)	R^2	NLL
Naïve	1.08 ± 0.13	0	-	-
QSPR (Moss and Cronin 2002)	1.46 ± 0.28	-34.71 ± 18.45	0.21 ± 0.21	-
QSPR (Potts and Guy 1992)	5.75 ± 1.14	-430.3 ± 74.38	0.18 ± 0.22	-
SLN 2f	1.07 ± 0.17	1.54 ± 4.11	0.21 ± 0.16	-
MIXEXP 2f	1.03 ± 0.14	4.76 ± 6.76	0.28 ± 0.12	-
GP 2f	0.98 ± 0.11	9.85 ± 5.92	0.32 ± 0.13	3.06 ± 0.48
SLN 5f	0.87 ± 0.12	20.12 ± 5.37	0.50 ± 0.12	-
MIXEXP 5f	0.44 ± 0.24	59.28 ± 22.03	0.81 ± 0.10	-
GP 5f	0.30 ± 0.07	72.62 ± 5.03	0.86 ± 0.05	1.48 ± 0.13

From Table 4.2, it can be seen that SLN, Mixture-of-Experts and GP demonstrated an improvement on the naïve predictions. The SLN approach, which is a simple linear regression model, although performing better than the two QSPR models, still appeared to have a relatively poor predictive capacity. This is due to the fact that SLN is the simplest kind of feed-forward network. This type of network is widely used for linear separable problems, but like a neuron, single layer networks are not capable of classifying nonlinear separable datasets. The regression coefficient obtained by the SLN 2f model (R^2 = 0.21) and by the SLN 5f model (R^2 = 0.50) was rather small, implying a great variability in the models developed when compared to the other QSPRs described in Table 4.2. By comparing the results obtained from the models incorporating either 2 or 5 features (Section 4.3.1), it can be seen that the SLN, Mixture-of-Experts and GP modelling methods have an improved performance when using five features rather than two. This would suggest the importance of including these additional terms – i.e. the solubility parameter and the two hydrogen bonding descriptors – in the prediction of percutaneous absorption. As a result of incorporating these additional inputs in the models, the predictive ability of these models increases, as reflected by the increase in the corresponding regression coefficients. The importance of solubility parameter as well as hydrogen bonding descriptors in percutaneous absorption has been discussed in detail in Section 2.3. Of the models summarised in Table 4.2, the GP 5f model produced the highest correlation coefficient (R^2 = 0.86). The machine learning methods showed that models with five features had a much better predictivity than those obtained using only two features, when considering NMSE, ION and regression coefficients. The GP model with 5 features produced the lowest upper quartile, median and lower quartile values on NMSE. (The terms NMSE and ION are fully described in Sections 4.3.5.1 and 4.3.5.2.)

A comparison of the data presented in Tables 4.1 and 4.2 shows that the GP 2f model developed with the use of human skin data – Group A18 (containing 142 compounds) provided a much better predictivity than the GP 2f model produced from the analysis of Group A19 (containing 149 chemicals). This could possibly be due to the fact that Group A19 contains, apart from human permeability coefficient data, 7 additional data points which had been derived using pig skin. This could have induced more variability in the data and, thus, generated a less robust model in terms of statistical fit. Even though pig skin is, in terms of structure, close to the human skin, its use to generate permeability data might nevertheless affect the statistical fit of the resulting GP model.

A comparison of the correlation coefficient values as well as the values for NMSE and ION supported this finding. It was found that when the GP 5f and the GP 6f models were compared, it was the GP 5f model that provided the better regression coefficient (Tables 4.1 and 4.2). This means that the inclusion of the sixth parameter, that is Melting Point, induces a greater variation into the model. Therefore, it can be concluded that the GP 5f model posseses the highest stability in predicting percutaneous absorption.

Figures 4.6 and 4.7 graphically summarise the respective ION performance parameters of the models developed in these studies.

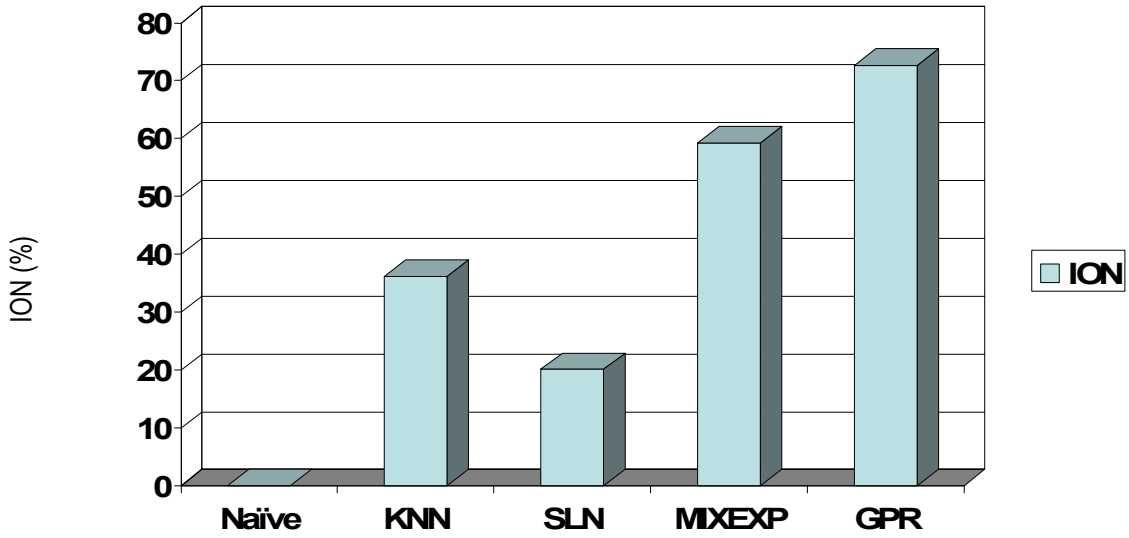


Figure 4.6. ION (%) results of test sets using different machine learning methods with 5 features (MW, log P, SP, Ha, Hd).

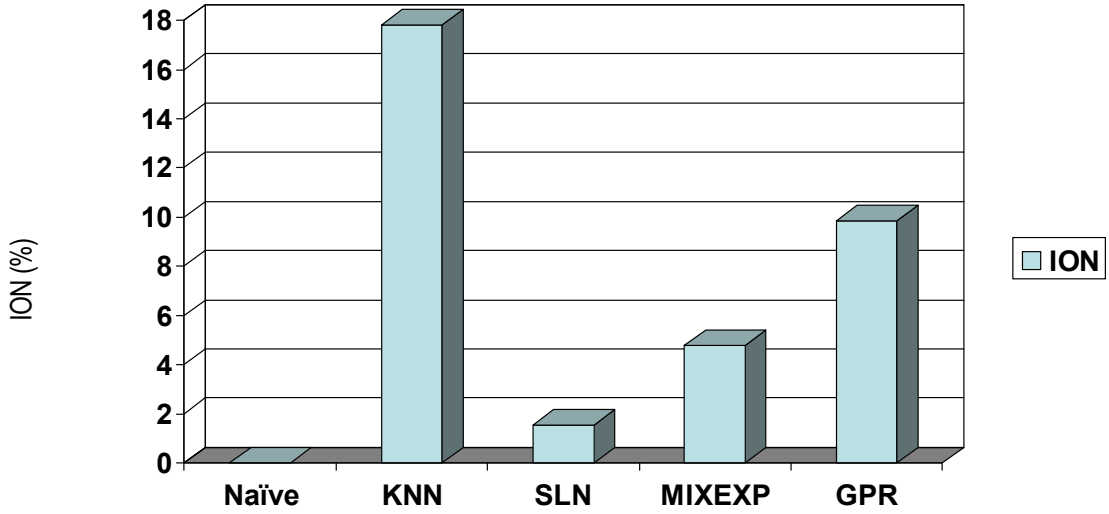


Figure 4.7. ION (%) results on test sets using different machine learning methods with 2 features (MW and log P).

As stated in Chapter 1, the vast majority of developed QSPR models have employed molecular descriptors, such as molecular weight and log P, in a linear fashion. The main advantage of such QSPR models is that they are simple to use. However, the use of these linear approaches often leads to a loss of critical information and results in models with poor predictive abilities. Some of the existing QSPRs models have used nonlinear methods (Table 4.3), with the view of providing more descriptive approaches to the percutaneous absorption of compounds. These nonlinear models have shown high regression coefficient values when predicting permeability coefficient values but the nature of the data employed for their development is to some extent uncertain (Sun et al. 2008). The nonlinear models available in the literature were either based on smaller and sometimes less diverse datasets or the data upon which these were developed were of poor quality (Neely et al. 2009).

Table 4.3. Models developed based on nonlinear data.

References	Data	R^2	Model	Descriptors
Pannier et al. (2003)	94	0.82	Fuzzy	MW, P_{ow}
Pannier et al. (2003)	37	0.97	Fuzzy	Log P_{ow}, H-bond donor
Pannier et al. (2003)	54	0.95	Fuzzy	Log P_{ow}, H-bond donor
Degim et al. (2003)	38	1.00	ANN	MW, P_{ow}, partial charge
Neely et al. (2009)	168	0.90	ANN	P_{ow}, polarity parameter, number of single bonds, melting point, nArCOOR (number of esters / aromatic), nQC (number of quaternary C), nHDon (number of H.donor), nRCOOR (number of esters / aliphatic), WHIM descriptors

An examination of the data in Table 4.1 shows that in terms of the descriptive statistics, the SLN 6f and GP 6f models provided a higher regression coefficient than the model developed by Moss and Cronin (2002). This is likely to be due to the nature of the datasets employed. The inclusion of highly lipophilic and hydrophilic compounds into the dataset produces an inherent Gaussian distribution of data (Figure 4.1). The results obtained from canonical correlation analysis, again demonstrated the existence of nonlinearity in the data, suggesting that nonlinear methods of analysis, such as GP models, would be the most appropriate in accurately predicting skin absorption.

While developing the GP and SLN models, as well as the other QSPRs, summarised in Tables 4.2 and 4.3, the effect of particular physicochemical descriptors on the resultant models was also investigated. The models developed using six molecular descriptors performed significantly better than those developed with two descriptors. This clearly suggests that the existence of Fedors' solubility (SP) and hydrogen bonding and melting point can affect the rate of penetration of compounds through skin and these parameters may exert a significant influence on the statistical robustness of the resulting models.

Fedors' solubility, as already described in Chapter 2, relates the solubility of a penetrant to the solubility of the stratum corneum, the skin barrier. It is effectively used to examine whether the solubility of one compound matches a solvent or another compound. The closer the two values of Fedors' solubility are, the more compatible (i.e. mutually soluble) they are likely to be. Furthermore, the inclusion of hydrogen bonding as a predictive descriptor into the equation plays an important role in model development.

Hydrogen bonds are specific non-covalent bonds between a hydrogen atom on one molecule and a highly electronegative atom on a different molecule. Commonly, H-bonding is likely to occur between hydrogen and, normally, oxygen, nitrogen and fluorine atoms, amongst others. Hydrogen bonding may affect percutaneous absorption by producing non-covalent bonds with the skin proteins. Specifically, the polypeptide chains of the protein are arranged in parallel sheets held together by hydrogen bonding**.** In the prediction of percutaneous absorption, both the method used to derive a model and the physicochemical descriptors of the model have varied significantly despite the perception of the applicability of the generic algorithm associated with work by Potts and Guy (1992). Indeed, Potts and Guy subsequently reanalysed the dataset associated with their initial work and found that, for a subset of the dataset, hydrogen bonding played an important role for the prediction of skin permeability for a specific class of molecules. Roberts et al. (1977b) first suggested that the passage of

a permeant through skin was related to its H-bonding capacity, expressed simply as the number of H-bonding groups present in the molecule, and the size of the molecule as defined by its molecular weight. It was shown that the introduction of even one hydrogen-bonding group to a molecule resulted in a substantial decrease in permeability, whilst the addition of further groups resulted in further decreases, which were nonlinear. In general, it was found that acids diffused more slowly than alcohols or phenols and this suggested that hydrogen bonding has a dominant effect on diffusion across the stratum corneum but a smaller influence on partitioning, where lipophilicity (i.e. log P) was more dominant.

As already discussed in Section 4.3.1, Barratt et al. (1995) proposed that melting point, combined with log P_{ow}, was a measure of aqueous solubility. Inclusion of the melting point decreased the statistical fit of the GP model. Consequently, melting point was not included in the second analysis (Group A19).

With regards to the second dataset analysis (149 compounds, Group A19), the data were represented as a bell-shaped curve or Gaussian curve when considering permeability as a function of specific molecular descriptors such as log P. An examination of the data in Table 4.2 indicates that the original model by Potts and Guy (1992) provided the least accurate fit compared with the derived models, such as the GP model. GP model was found to provide the best fit in terms of statistical validation. Furthermore, Table 4.2 shows that while other QSPR models are comparatively poor compared with the GP model, they are statistically more applicable than the Potts and Guy (1992) model in terms of NMSE, for example. Gullick et al. (2008) discussed predictions of skin permeability from a range of models and indicated that conventional QSPR models clearly failed to provide accurate predictions of experimental results at higher log P values. This may lead to the conclusion that, as the relationship between skin permeability and molecular properties is nonlinear, the use of nonlinear models is not only valid but wholly appropriate, reflecting the true nature of skin absorption for a wide range of exogenous penetrants. This is clearly reflected in Figures 4.1 and 4.2 that demonstrate the underlying nonlinear nature of the dataset.

The Gaussian model developed was dependent upon the availability of well-defined parameters that were carefully screened prior to use. The prediction of permeability is generated only from data within the range of the model. The Gaussian Process model, as it is applied in machine learning, is an attractive way of carrying out non-parametric Bayesian modelling in a supervised learning problem and given that the model can be easily and rapidly improved by the addition of new data points, the GP can effectively learn every time additions are made to the dataset. Also, under the Gaussian process the models are easier to handle and to interpret compared to previously-developed nonlinear models, such as those using artificial neural networks and neuro fuzzy networks (Li et al. 1999).

However, it must be noted that the GP model currently developed posseses the following limitation: It does not employ log D as an input, but rather log P values. As a result, the ionisation effect is not being taken under consideration in the prediction process of the GP model. In other words, scientists should consider for future reference to incorporate log D values in the GP models instead of using log P values.

4.5. CONCLUSION

The statistical validity of the GP, SLN and QSPR models was determined and compared, indicating the superiority of GP models in terms of statistical accuracy. GP models produce better results, including better predictions of experimental targets and statistical performance measures, than QSPRs models and naïve predictions when applied to human skin data (Tables 4.1 and 4.2). Additionally, the effect of particular physicochemical descriptors on the resultant models was also investigated. The models developed using five molecular descriptors (log P, MW, Ha, Hd, SP) performed significantly better than those developed with two descriptors (log P and MW). Again, this clearly suggested the importance of including Fedors' solubility (SP) and hydrogen bonding as potential penetrants into the algorithm under construction. Furthermore, it has to be noted that when the melting point was eliminated from the equation, the trend was the same, with 5f models being again statistically better than 2f models. Melting point may be an important input and useful while predicting equations, but cannot be considered as a determinant factor, such as MW or lipophilicity. Statistically speaking, the melting point coefficient was found to be smaller than the log P coefficient in all GP models. Furthermore, by increasing the number of data in the dataset, i.e. from 142 to 149 chemicals, the results were not found to be the same. The statistical fit of the models developed decreased, suggesting that even though it were pig skin data that were added, still Group A19 (Appendix 5, Group A19) was 'diluted,' possibly due to species variation. As already discussed in previous chapters, the quality of the input plays a crucial role in model development processes and therefore special attention should be given to the selection of data prior to any model development or related action by the modellers seeking to develop well defined and accurate algorithms.

The GP model, derived from the use of 5 inputs, has yielded a predictive model that provides a significantly more accurate estimate of skin absorption than previous models across a wider range of molecular properties. It is particularly capable of providing excellent predictions where previous studies have shown QSPRs to fail: at high log P and MW of penetrants. The results presented indicate that, in terms of statistical performance, the following rank order was observed in the effectiveness of log K_p predictivity of the respective models: GP > SLN > QSPR. This rank suggested that statistically, a nonlinear approach is more appropriate for analysis of the dataset employed herein than linear techniques (as used in many QSPR methods), since the GP method demonstrated that there was a greater confidence in the predictive outcome of this model compared to other methods.

In Chapter 4, it has been indicated that the GP method may be more directly applicable to the prediction of percutaneous absorption than the widely-used conventional QSPR methods. The GP model presented here for skin permeation represents an improvement on the models in the literature in several aspects, including the use of a well-screened and refined dataset consisting of diverse chemical structures as well as the use of nonlinear transformations to obtain the most suitable set of descriptors. The next step would be the true external validation by application of the developed models on external data. Specifically, the evaluation and validation processes are the most important conditions for application of models obtained by data mining. The accuracy and the reliability of the GP model have yet to be established. Consequently, it is important to

determine the predictive accuracy of the GP model by comparing actual experimentally derived values to those predicted by the model. However, as already mentioned earlier in Chapter 4, the developed GP model presents one basic limitation, since it does not take under consideration the ionisation effect as a factor affecting the permeability coefficient. Clearly these factors require further investigation and form the basis of the studies described in the following chapter.

Chapter Five

A Mathematical / Computational Model to Predict Drug Absorption across the Skin

5.1. INTRODUCTION

5.1.1. Validation of Linear and Nonlinear Models

The final step of model development is to verify the patterns produced by the data mining algorithms and accommodate real data, generated experimentally. Generally speaking, not all patterns found by the developed algorithms are necessarily valid (Lemke et al. 2002) and hence the evaluation and validation processes are important conditions for the application of models obtained by data mining. The accuracy and the reliability of the final models have to be established. Therefore, it is of importance to assess the predictive capacity of the nonlinear GP model together with the 5f linear model and hence for validation purposes it was planned to investigate the diffusion *in vitro* of a range of compounds across isolated skin under carefully controlled conditions. The nonlinear GP model was chosen because of its novelty and the 5f linear model because it was the only model resulting from the 'high quality' data generated from Groups A18 and A19. Models developed upon Groups A1 to A17 (described in Chapter 3) were based on far too little data to be considered predictive enough to justify validation. Differences in the protocols used for measurement of percutaneous penetration have resulted in the collection of values that are not wholly consistent and this often needlessly introduces an unwanted degree of variability in the resulting models. To limit such variation, all permeation experiments in this study were to be conducted under prescribed and carefully controlled conditions in order to seek to match the parameters used in the development of the GP model. Additionally, the effect of ionisation on permeability would be taken into consideration by determining the flux of a single ionisable drug at three different pH values. It has to be appreciated that both models have certain limitations. For example, the GP model, as developed, does not take into account the log D values in its determinations but rather incorporates the log P values. In addition, the 5f model is based on a linear model. Nevertheless, as discussed in Chapters 3 and 4, both models have been developed from carefully-selected data and suggest the generation of robust predictions, in terms of statistical fit.

5.1.2. Ionisation Effect

One of the issues that has not been adequately considered in the development of earlier models is the effect of pH on permeability. Most of the clinically-accepted drugs for delivery through the skin are of low molecular weight, lipophilic and effective at low doses. However, the majority of these drugs comprise weak acids or bases, which are ionised under normal physiological conditions. The human stratum corneum acts as a barrier to the skin penetration of charged species and other biological membranes as well as non-porous polymers generally provide a similar barrier (Sarveiya et al. 2004). The permeation coefficient of such species has been estimated to be about 104 times smaller than for the respective uncharged analogues (Lee et al. 1985).

As already discussed in Chapters 1 and 3, the use of the distribution ratio D rather than log P is preferable in the context of ionisable molecules, since the partition coefficient P refers to the concentration ratio of a single species, whereas the distribution coefficient D refers to a collection of species and is pH-dependent. The

distribution ratio D is used only in the context of ionisable molecules; otherwise D and P are the same value. Even though the distribution coefficient is a more relevant parameter for ionisable molecules, less effort has been applied to its assessment. Knowledge of the distribution coefficient and pKa is important for the basic characterisation of a compound, particularly when assessing the compound's potential to penetrate biological or lipid barriers (Lipinski et al. 2001). Although distribution coefficients are not entirely representative of permeability through skin, or other tissues, they are related, with the distribution coefficient being a key factor in determining the permeability of drugs through lipid barriers (Scott & Clymer 2002). The distribution coefficient depends only on pH, pKa values and P (not on concentration) of the sample species. The relationship that best describes permeability in terms of log D was detailed earlier in Chapter 3. This linearly-developed model (Equation 3.12) was derived by the use of published log D values (Avdeef 2003), which was subsequently validated by determining the permeability of some compounds experimentally and comparing the values so obtained with those predicted by the model.

5.1.3. Drug Selection

In seeking to develop a QSPR, the choice of certain compounds as outliers and their exclusion from such datasets can greatly influence the apparent quality of the final model since the latter will be based on the remaining data points. In most cases, the outliers represent both ends of what is effectively a Gaussian-type distribution. Consequently, when these are eliminated from the datasets, the resulting models tend to lose their statistical power, as they fail to represent fully the apparently nonlinear relationship between the physicochemical parameters of molecules and their permeability across skin. In order to assess the developed nonlinear model, different lipophilicity ranges were used in the evaluation process. Specifically, the applied experimental design involved the selection of drugs with different lipophilicities, whilst their applicability as potential model penetrants to test the validity of the developed mathematical models was reviewed. Table 5.1 indicates potential drug candidates that encompass 3 different lipophilicity ranges. The first three drugs were of low lipophilicity ($-1 < \log P > 1$), the fourth one was of intermediate lipophilicity ($1 < \log P > 3$) and the last one was selected due to its high log P value ($\log P > 3$).

Even though molecular weight is also a very important factor when considering transdermal delivery, in order to avoid any possible influence of this factor on preliminary work, relatively small molecules, with molecular weight less than 350 Da, were selected.

Table 5.1. Drug candidates.

Name	pKa	Log P	MW
temozolomide	-	-0.99	194.2
procaine HCL	8.90	-0.84	272.8
paracetamol	9.38	0.27	151.2
furosemide	3.90	2.32	330.7
ibuprofen	4.45	3.79	206.3

Other factors such as structural diversity, commercial availability, price and the availability of a suitable analytical technique for quantification were considered as additional selection criteria. Additionally, the presence of specific ionisable groups within a structure was a prerequisite in the drug selection to enable the effects of ionisation to be studied. The structures of the selected compounds are shown in Figure 5.1. Ibuprofen is a Non-Steroidal Anti-Inflammatory Drug (NSAID) that has been formulated into a number of topical preparations and its solubility and diffusion parameters as a function of pH have been documented earlier (Watkinson et al. 1994; Hadgraft & Valenta 2000). It has ionisable groups, a simple structure, is of low cost and its permeation over a range of pH through human skin is available in the literature (Watkinson et al. 1993; Valenta et al. 2000). Accordingly it appeared to provide an ideal drug to investigate the importance of pH in model development.

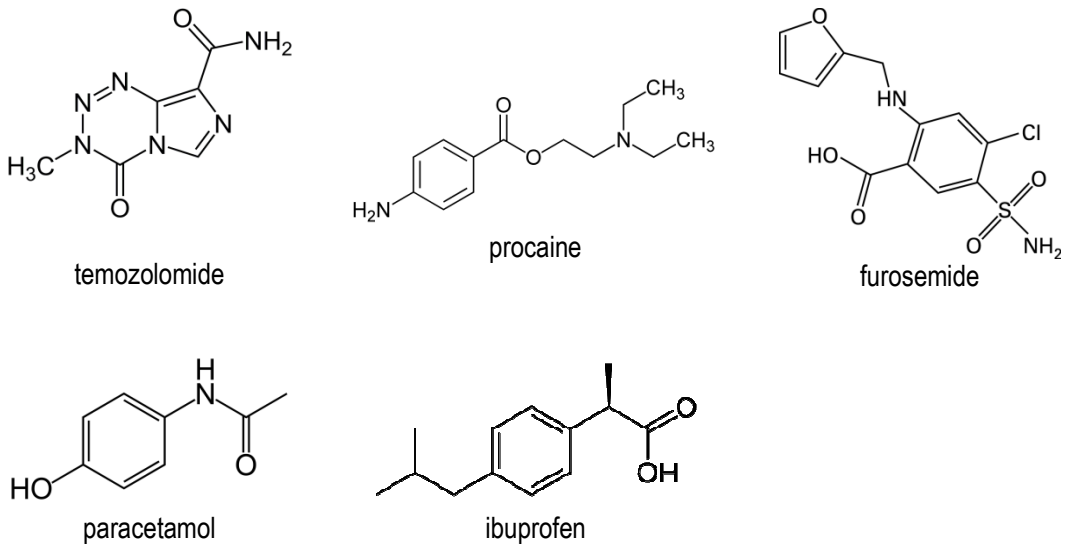


Figure 5.1. The structures of compounds selected for the determination of skin permeability coefficients.

5.2. AIMS AND OBJECTIVES

The aim of this *in vitro* study was to seek to investigate the relative accuracy of the GP, 5f linear regression and linear ionisation models. For comparison purposes it was also planned to use the data to reanalyse the Potts and Guy (1992) model. One further aim was to obtain permeation data under carefully controlled conditions and seek to correlate these with values calculated from the application of various models. For the purpose of the validation process, apart from comparing the experimental with the predicted values, the structural deviation and degree of fit to each model would be determined.

Thus, the primary objective was to measure the fluxes of several compounds having a range of log P values between -1 up to 4 across isolated epidermis using the Franz Cell technique and to compare these fluxes to those predicted by the models. The secondary objective was to assess the effect of ionisation on permeability by determining the flux of a single ionisable drug at three different pH values, but otherwise maintaining the same experimental conditions. While conducting the initial experimental

work, the ionisation effect was not controlled, as the purpose at that point of the research was to perform a simple flux measurement. However, by the time the importance of the second objective of Chapter 5, i.e. the effect of ionisation, was recognised, the GP model had already been developed.

5.3. METHOD

5.3.1. Materials

The model drugs temozolomide (≥98%), furosemide (≥99%), paracetamol (≥99%), procaine HCL (≥97%), ibuprofen (≥98%) were all obtained by from Sigma Aldrich (O.M.) Ltd. (Greece) and were analysed by HPLC with a UV detector. Table 5.2 provides the suppliers of other materials that were used in the experimental work.

Table 5.2. Materials employed in the current study.

Materials	Supplier	Address
acetic acid (HPLC grade)	Fisher Scientific UK Ltd	Loughborough, UK
citric acid	Chemika / Biochemika Fluka Chemie AG	Buchs, Switzerland
potassium phosphate monobasic	Chemika / Biochemika Fluka Chemie AG	Buchs, Switzerland
sodium dihydrogen phosphate	Sigma-Aldrich (O.M.) Ltd	Dorset, UK
sodium phosphate dibasic dihydrate	Chemika / Biochemika Fluka Chemie AG	Buchs, Switzerland
ethanol (absolute)	Hayman Ltd	Essex, UK
acetone (HPLC) grade	Fisher Scientific UK Ltd	Leicestershire, UK
methanol (HPLC grade)	Fisher Scientific UK Ltd	Leicestershire, UK
acetonitrile (HPLC grade)	Fisher Scientific UK Ltd	Leicestershire, UK
distilled water	Millipore Water Purification System	Hertfordshire, UK
PEG 40%	Fisher Scientific UK Ltd	Leicestershire, UK
isopropyl alcohol	Sigma-Aldrich (O.M.) Ltd	Dorset, UK
chloroacetic acid	Sigma-Aldrich (O.M.) Ltd	Dorset, UK

5.3.2. Methods

5.3.2.1. HPLC Analysis

Chromatographic measurements were carried out using a Hewlett-Packard HPLC System, quaternary pump with autosampler connected to a DAD detector. The assays used were based on those previously reported in the literature (Table 5.3). The column used was C18 5 μM 15 cm x 4.6 mm (Discovery HS). A series of different isocratic conditions were employed in the assays.

Table 5.3. HPLC conditions employed to assay candidate penetrants.

Name	Solvent	Mobile Phase	Wavelength (nm)	Flow rate ($mLmin^{-1}$)	Inj. vol. (µL)	References
temozolomide	distilled water	0.5% acetic acid: methanol (90:10)	330	1.0	200	Suppasansatorna et al. (2006)
procaine HCL	PBS (0.1 M)	1% acetic acid: methanol (60:40)	254	1.1	5	Wang (1983)
	PBS (0.1 M)	methanol:PBS (2:1)	220	1.0	50	Grouls et al. (1997)
	PBS (0.1 M) : water (20:80)	methanol:PBS (2:1)	220	1.0	50	Grouls et al. (1997)
paracetamol	aqueous ethanol (10%)	water:methanol (3:1)	245	0.5	20	Sintov et al. (2003)
	aqueous ethanol (10%)	0.01 M KH_2PO_4 : methanol : acetonitrile : isopropyl alcohol (42:20:30:30)	215	1.0	10	Altun (2002)
	PBS (0.1 M)	0.01 M KH_2PO_4 : methanol : acetonitrile : isopropyl alcohol (42:20:30:30)	215	1.0	10	Altun (2002)
furosemide	40%PEG 400	0.01 M KH_2PO_4 : methanol (70:30)	229	1.2	50	Agyralides et al. (2004)
	40%PEG 400	acetonitrile : 0.05M NaH_2PO_4 (25:75)	220	1.4	20	Guzman et al. (2003)
ibuprofen	PBS (0.1 M)	acetonitrile : phosphate buffer pH 3.2 (65:35)	225	1.2	20	Hadgraft et al. (2000a)
	PBS (0.1 M)	chloroacetic acid 1% : acetonitrile (40:60)	254	2.0	100	Phuong Truong, Application Note SI-01028

Standard concentrations of the model penetrants (0.1-100 μgml^{-1}) were used. Specifically, stock solutions of 1 $mgml^{-1}$ were initially prepared and standards were made by (serial) dilution of these solutions. For example a standard sample of 50 μgml^{-1} was prepared by diluting 0.5 ml of the stock solution into 10 ml of a solution. The response of the analytical procedure for these standards was measured. The average response of the blank samples (samples with no analyte being included) was subtracted from that obtained from each measured standard. Calibration curves comprising peak area plotted as a function of drug concentration were constructed for each compound and a good linearity was established, as determined from linear regression analysis. The constructed curves were then used to quantify the concentration of the respective compounds in the unknown samples. Both the Limit of Detection (LOD) and the Limit of Quantification (LOQ) were determined in the results section (Table 5.7) from Equations 5.1 and 5.2 (MacDougall et al. 1980), without the use of a blank but rather by using the slope of the calibration curve and obtaining the standard error of the intercept.

$$LOD = (STEYX / Slope)*3.3 \quad \text{(Equation 5.1)}$$

$$LOQ = (STEYX / Slope)*10 \quad \text{(Equation 5.2)}$$

5.3.2.2. HPLC Validation

For validation purposes, throughout the experimental work and before each measurement took place, fresh calibration curves were constructed using standard drug concentrations (n = 8). Three samples were analysed from each standard each time. The range of all the calibration curves and the method of construction is described in the previous section. The system was always calibrated prior to each assay and the relevant limits of detection were redetermined. Additionally, the % precision and % accuracy between the HPLC calibration measurements which were determined from calibration standards run for each drug and for each assay to cover all solubility, stability and permeation experiments were determined (Appendix 23).

5.3.2.3. Preparation of Epidermal Sheets

Fresh, surgically excised samples of healthy human skin were obtained directly after abdominoplastic surgery with informed consent from a patient attending a private clinic in Athens, Greece. The board of directors and the ethics committee of the clinic reviewed the Informed Consent Template created by the University of Hertfordshire (Appendix 20) and approved it. A signed copy of the informed consent was retained by the investigator for the purpose of this project and a further copy was provided to the patient. The skin sample was sent to the UK accompanied with the signed informed consent form and a document signed by the responsible physician stating that the sample was HIV and hepatitis free. The donor was a female, 45-year-old non-smoking white European. Subcutaneous fat was carefully removed from the skin sample using forceps and a scalpel, the epidermis was isolated and then was stored in a freezer at -20 °C. The epidermal membrane was isolated from full-thickness skin by a heat separation method. Water was heated in a beaker to 60°C and the full-thickness skin suspended in the water with forceps for 60 seconds before gently peeling the epidermis from the dermis using forceps.

5.3.2.4. Solubility Studies in Donor Solution

The solubility of each compound in the selected solution was determined by placing an excess amount of each of the candidate penetrants into vials containing the corresponding solvent (Table 5.4) and these were sealed with parafilm. Each suspension was stirred overnight at 37 °C using a magnetic stirrer and follower bar. At different time points (0, 30, 60, 120, 180, 300 min), a sample (500 μL) was withdrawn from each vial, filtered using Whatmann 0.22 μm and diluted according to the schemes summarised in Table 5.4 and then immediately analysed by HPLC. The solubilities were calculated from the data points after equilibrium was established.

Table 5.4. Dilution factors used in the determination of solubility of candidate penetrants.

Name	pH of the solution	Solvent / receptor fluid	Dilution factor
temozolomide	6.5	distilled water	1000
procaine HCL	7.4	PBS	100000
	7.2	PBS : water (20:80)	100000
paracetamol	6.9	aq. ethanol	10000
	7.1	10% aq. ethanol	1000
	7.3	PBS	1000
furosemide	6.8	40% PEG 400	1000
ibuprofen	7.4	PBS (pH 7.4)	1000

5.3.2.5. Solubility-pH Profile

An excess of ibuprofen was added to phosphate buffer containing media and the pH fixed at values of 2.6 and 4.2 (Table 5.5) in screw-capped vials containing the corresponding solvent and these were sealed with parafilm. Each suspension was allowed to stir overnight at 37 °C. At different time points (0, 0.30, 1, 2, 3, 5, 8, 24, 29, 32, 48 h), a sample (500 µL) was withdrawn from each vial. The solubilities were calculated from the data points when equilibrium was attained. The pH of the resultant mixture was determined during this period and adjusted to the required value by adding small amounts of citric acid or sodium phosphate as appropriate. All experiments were carried out a further two times.

Table 5.5. Solvents employed to dissolve ibuprofen at different pH values

Name	Solvent / receptor fluid	pH
ibuprofen	89.1 ml (0.1 M) citric acid & 10.9 ml (0.2 M) $Na_2 HPO_4$	2.6
ibuprofen	60 ml (0.1 M) citric acid & 40 ml (0.2M) $Na_2 HPO_4$	4.2

5.3.2.6. Stability Studies

5.3.2.6.1. Stability of Penetrants in Receiver Fluid under Specified Conditions

The chemical stability and recovery of each of the five selected penetrants in the corresponding receptor fluid was determined by incubating standards of known concentration at 37 ºC for a 48 h period, with samples being assayed after incubation for 0, 24 and 48 h and for temozolomide an extra time point at 8 h was included. Temozolomide samples were maintained at temperatures between 2 ºC and 8 ºC but subsequent work proved the unsuitability of this compound for study due to instability. Each penetrant was dissolved in a specific volume of receptor fluid at the concentrations shown in Appendix 21 and each resulting solution, of a specific volume, was transferred to a water bath at 37ºC. Aliquots, usually 0.75 ml volume, were removed and analysed using HPLC (Section 5.3.2.1). Triplicate samples of the above volume of solution containing each of the respective compounds were assayed with each compound being present at two different concentrations. The % recovery was calculated by expressing the final concentration as a percentage of the initial concentration. Appendix 21 shows for ibuprofen (pH 4.2) in detail the concentrations and volumes employed at each stage. For each experiment, both the receptor and donor fluids were always the same solvent.

5.3.2.6.2. Stability Studies with Spent Receiver Fluid

Spent receiver fluid was prepared by recovery of the fluid after incubating a layer of skin for 48 h in using Franz cells (volume = 10 ml). Franz cells were filled with receptor fluid and a section of human skin (Section 5.3.2.3) with diameter approximately 2 cm^2 was sandwiched between the donor and receiver compartment (Section 5.3.2.7). To limit the evaporation of the fluid, the chamber was sealed with parafilm. The receiver solutions were stirred constantly with a magnetic stirrer at 37 °C for 48 h and the resulting generated 'spent'

receiver fluids were then transferred to separate bottles and solutions of the penetrants introduced. The chemical stability and recovery of each penetrant in the corresponding spent receiver fluid was determined by incubating standards of known concentration in the receptor solution at 37 °C for a 48 h period. Each penetrant solution was stored in a thermostated water bath at 37 °C and aliquots were then removed and analysed via HPLC at 0, 24 and 48 h. The amount of compound introduced is reported in Appendix 21. Three samples of each compound were investigated for their stability at different concentrations.

5.3.2.7. Franz Cell Experiments

The method employed in these experiments was based on the 'perfect' experiment methodology and was based on the guidelines list available in OECD guidelines (2004a, 2004c). The study involved the use of epidermal human skin tissue mounted in a Franz-type diffusion cell [Frantz et al. (1995); Figure 1.8]. The donor and receiver chamber were secured with a spring and this was strengthened by wrapping the joint between the two cells with Parafilm®, so as to prevent leakage of the contents.

5.3.2.7.1. Preliminary Study

Preliminary studies indicated that ibuprofen, paracetamol, procaine HCl and furosemide had sufficient stability in solution to be used in the Franz cell experiments. To determine the absorption profile of each penetrant, feasibility preliminary release studies were conducted as follows prior to the main cohort of experiments using cells with a receptor compartment containing approximately 2 ml.

Three Franz cells of 2 ml volume each were selected for use for each compound (n = 3). However, due to limited availability in abdominal skin, small Franz cells of an average cross sectional area of 0.6 cm^2 and a volume of 2 ml were selected. The excised human skin (epidermal sheet) obtained from the abdominal region was mounted between the donor and the receptor compartment of the Franz cell. The receptor compartments of the Franz cells were then filled with the receptor fluid. Prior to application, the receptor fluid was sonicated to remove dissolved oxygen. The receptor solutions were stirred continuously with a magnetic stirrer and the water bath was maintained at 37 °C. The Franz cells containing epidermis were equilibrated with the receiver fluid in the water bath overnight at 37 °C. Fresh receiver fluid was placed into the receptor compartment and it was allowed to equilibrate for 1 h prior to the application. To avoid air bubbles being developed inside the receptor compartment, the cell was turned upside down while the receptor fluid application was introduced via the side arm. A volume of 0.8 ml of donor suspension (C_{max}) was applied to the surface of the skin and 200 µL of the receiver fluid were removed via sampling from the receptor cell at 0, 1, 2, 4, 8 and 24 h and then analysed via HPLC (Section 5.3.2). The donor suspension was prepared by adding the medication under investigation to the donor vehicle until its solubility limit was reached (Appendix 21). After the removal of each sample, an equal volume of prewarmed receptor fluid (37 °C) was replaced with an equal volume of prewarmed solvent. The concentration of diffusant in each sample was determined by reference to freshly prepared calibration samples. Following the preliminary

experiments, the actual permeation experiments were conducted using suitable time points derived from the feasibility studies. The methodology employed was exactly the same as that followed when conducting the preliminary studies.

5.3.2.7.2. Full Study

Similarly to the preliminary experiments and prior to the initiation of each set of experiments, six small Franz cells of the same size (cross sectional are 0.6 cm^2 and containing a receptor volume of 2 ml) were employed. For each compound, the receptor compartments of each Franz cell were filled with degassed receiver fluid and a piece of epidermal human skin (Section 5.3.2.3) was sandwiched between the donor and the receiver compartments. A small Teflon-coated magnetic stirrer bar, 25 mm in length and 2.5 mm in diameter, was included in the receiver compartment so that stirring (at a rate of 5 rpm) occurred throughout the duration of the experiment. To avoid air bubbles developing inside the receptor compartment, the cell was turned upside down while the receptor fluid was introduced via the side arm. The cells were left to equilibrate overnight on a stirring plate submerged in a water bath maintained at 37°C. The following morning, a sample of receiver fluid (approximately 2 ml, depending on the exact size of the cell) was withdrawn from each cell and the cells were filled with fresh degassed receiver fluid. The experiments were initiated by applying a concentration of 20% above C_{max} (i.e. a saturated suspension of the drug in donor fluid) to the skin in the donor chamber (0.8 ml instead of a concentration of the drug corresponding to C_{max}, i.e. a saturated suspension). The pH of each suspension was adjusted during the experiment to maintain it at a constant value, as this was monitored using a pH meter. Similarly, samples (2 ml) were then removed at prescribed time intervals. After sampling, the receiver fluid was immediately replaced with the same volume of prewarmed, fresh degassed receiver fluid in order to maintain the volume in the Franz cell and the samples were analysed via the HPLC method. Table 5.6 illustrates exact concentrations applied on the surface of the skin in the donor chamber.

Table 5.6. Dosing solutions - concentrations.

Name	Vehicle	Cs +20% ($mgml^{-1}$)
procaine HCL	PBS: water (20:80)	7973.21
paracetamol	PBS	0.50
furosemide	40% PEG 400	15.84
ibuprofen (pH 2.6)	89.1 ml (0.1 M) citric acid & 10.9 ml (0.2 M), $Na_2 HPO_4$	0.07
ibuprofen (pH 4.2)	60 ml (0.1 M) citric acid & 40 ml (0.2M), $Na_2 HPO_4$	0.78
ibuprofen (pH 7.4)	PBS	6.08

The choice of donor solution was based on what was available in the literature. Ionisation was only recorded and not controlled since, in the majority of published experiments, ionisation is not controlled either.

5.3.2.8. Data Analysis and Statistical Analysis

The cumulative amount of penetrant, Q ($\mu g cm^{-2}$), which permeated the skin per unit surface area was plotted as a function of time. The linear portion of the plot (which included five data points) was taken as being the steady state flux (Js). The permeability coefficient (K_P) was calculated with Equation 5.3:

$$K_P = Js\ C_v \qquad \text{(Equation 5.3)}$$

where C_v is concentration of the penetrant in solution of the applied suspension.

The same volume of fresh (prewarmed) medium was introduced into the receptor compartment after removal of each sample and the concentration of penetrant corrected cumulatively for the concurrent dilutions and the removal of drug in the previous samples. Experimental data presented represent the mean values ($n \geq 4$) and standard deviation (SD). Statistical analysis of J and K_p was performed using a one-way analysis of variance (ANOVA) to determine any differences between the means of experimentally determined values, with significant differences being accepted when $P \leq 0.05$. The interlaboratory comparisons were evaluated by using the rejection of the outlying observations theory (Youden & Connor 1953). The rejection ratio (D / d) for each case was calculated (Equation 5.4).

$$\text{Rejection Ratio} = D / d > 20 \qquad \text{(Equation 5.4)}$$

where D is the difference between the most extreme observation and its closest neighbour and d is the measurement between two closest observations.

In order to determine that each set of data is normally distributed, the flux values obtained from each set of experiments were analysed for skewness and kurtosis as measures of asymmetry and long-tailedness of the data distribution, respectively.

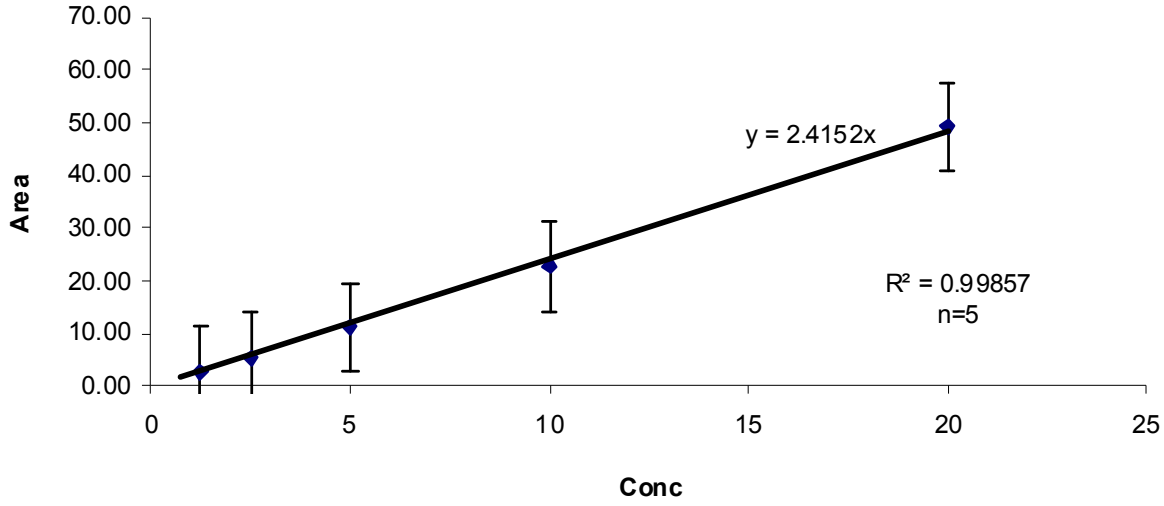
5.4. RESULTS

5.4.1. Calibration Curve Results

The accuracy of the analytical method was determined by comparing the results of the method obtained with the results reported from an established reference method. Furthermore, the linear relationship and the resulting correlation coefficient for ibuprofen are both shown in Figure 5.2. Samples of the HPLC traces and the resulting calibration curves for the other diffusants are presented in Appendix 23.

Table 5.7. LOD and LOQ values for a series of candidate penetrants.

Compound	LOD (μgml^{-1})	LOQ (μgml^{-1})	R^2
temozolomide	1.55	4.69	0.99
procaine	0.67	2.04	0.99
furosemide	0.45	1.36	0.99
paracetamol	0.06	0.19	0.99
ibuprofen (pH 2.4 / 4.2 / 7.4)	1.16	3.53	0.99



Sample	Conc (μgml^{-1})	Area (mAU.s)	Area (mAU.s)	Area (mAU.s)	Average Area (mAU.s)
1	40	95.44	93.30	94.21	94.32
2	20	47.41	53.06	47.41	49.29
3	10	22.83	22.83	22.61	22.76
4	5	11.35	11.19	11.24	11.26
5	2.5	5.26	5.66	5.63	5.52
6	1.25	2.75	2.60	2.88	2.75
7	0.75	1.71	1.68	1.70	1.70
8	0.375	1.38	1.33	1.35	1.35

Figure 5.2. A calibration curve for ibuprofen, plotting HPLC peak area as a function of ibuprofen concentration (mean ± SD; n = 5).

5.4.2. Normal Distribution of Data

The median k values fell within the 95% confidence interval for the mean, showing that these data were not skewed. The ratio of skewness to its standard error was compared to a standardised score from a normal distribution. The ratio of kurtosis to its standard error was also compared with a normalised score. All scores indicated that there were no short- or long-tailed distributions. Therefore, these results indicated that each dataset was normally distributed.

5.4.3. Drug Selection for Stability Studies

As already discussed in Section 5.1.3, the data upon which a model was developed play an important role in making it highly predictive. Apart from choosing molecules of various lipophilicities, structural diversities, price and commercial availability, it was important during the selection process to examine how well these molecules were being accommodated by the models under validation. Specifically, the selection was based primarily upon choosing a range of compounds that might be predicted by the individual models to have differing permeability. In order to predict the permeability capacity of each drug candidate, the respective molecular descriptors were analysed using the Potts and Guy (1992) and GP models.

According to the Potts and Guy (1992) model, the fastest absorbed species (highest flux) would be expected to be ibuprofen, whereas according to the GP model procaine HCl was predicted to be the fastest absorbed compound. These predictions are presented in Table 5.11. The GP model includes five descriptors in its algorithm as opposed to Potts and Guy (1992) model that uses only 2 features (molecular weight and lipophilicity) as molecular descriptors. The GP model was developed by randomly selecting 130 compounds from 149 (Group A19) compounds as training examples (termed the first training set) and training a GP model. Regarding the permeability coefficient values, the GP model predicted that paracetamol would have the smallest permeability coefficient value, in contrast to data obtained using the Potts and Guy (1992) model, where procaine HCl was predicted to have the lowest K_p value. Finally, both the GP model and the Potts and Guy (1992) equation predicted furosemide, the fourth drug candidate, to have an intermediate absorption profile compared to ibuprofen, paracetamol and procaine HCl.

5.4.4. Solubility Studies and Stability Studies

5.4.4.1. Solubility Studies

The saturated concentration of the five candidate drugs was determined in different media, which it was anticipated might be suitable to maintain sink conditions in the receptor phase throughout the diffusion process. Both the selected solvents and the respective solubilities are summarised in Table 5.8. One major criterion for the selection of the receptor phase was that the media should be compatible, in terms of physicochemical properties and structure, with isolated epidermis. At low pH, it is apparent that the solubility of Ibuprofen was much smaller than its solubility in higher pH environments. As the pH was decreased so was the degree of ionisation of the carboxylic acid residue. Thus, the solubility of ibuprofen (pKa 4.45) decreased from 5.066 $mgml^{-1}$ in PBS (pH 7.4) to 0.059 $mgml^{-1}$ at pH 2.6.

Table 5.8. Saturated Concentrations (Cs) of drug candidates in possible receptor media.

Name	Vehicle	Cs ($mgml^{-1}$)
temozolomide	distilled water	1.74 ± 0.79
procaine HCL	PBS: water (20:80)	6644.34 ± 708
paracetamol	PBS	0.42 ± 0.004
furosemide	40% PEG 400	13.20 ± 0.068
ibuprofen (pH 2.6)	89.1 ml (0.1 M) citric acid & 10.9 ml (0.2 M), $Na_2 HPO_4$	0.059 ± 0.0237
ibuprofen (pH 4.2)	60 ml (0.1 M) citric acid & 40 ml (0.2M), $Na_2 HPO_4$	0.65 ± 0.06
ibuprofen (pH 7.4)	PBS	5.07 ± 0.0237

* Values shown as mean ± SD. (n = 3)

Table 5.8 summarises the saturated concentrations of the drugs under investigation in a variety of media. Furosemide is practically insoluble in water and in dichloromethane but sparingly soluble in alcohol and soluble in acetone. It is also highly soluble in high concentrations of PEG 400 (Cho et al. 2005) and 10% PEG 400 was reported to act as a good solvent to obtain the permeability coefficient through human skin. Even though a permeability coefficient through human skin might have been obtained using PEG 10%, PEG 40% was employed in the current study because a higher solubility was attainable, thereby ensuring sink conditions in the receiver would be maintained for longer. The solubility of furosemide in 40% PEG in water solution was 13.2 $mgml^{-1}$ (Table 5.8). Temozolomide is soluble in a variety of solvents including distilled water (Zhou & Tan 2006), where the solubility was found to be 1.74 $mgml^{-1}$ (Table 5.8). Paracetamol is highly soluble in ethanol, but so as to limit the possible solvent depletion lipids from the skin, PBS was selected for use. For the purpose of screening and selecting suitable solvents for the receptor phase, it was assumed that no more than 10% of the applied drug would diffuse during the experimental period. For all compounds, this value (a second selection criterion), which was the projected final concentration had to be well above the LOQ of the HPLC assay. Ibuprofen is relatively non-polar and accordingly its highest solubility would be expected to be in solvents with lower solubility parameter values, such as acetone, ethyl acetate and lipophilic alcohols. However, by replacing the acidic proton with sodium, the region of maximum solubility is shifted to larger solubility parameter values as compared to the parent acid (Bustamante et al. 2000).

As expected, the solubility of ibuprofen sodium (pKa 4.45; Avdeef et al. 1998) increased with increasing pH (Table 5.8). The solubility of a substance in a given solvent is defined as the concentration of the dissolved substance in equilibrium with a saturated solution, with generally polar substances dissolving well in polar solvents and non-polar substances dissolving in non-polar solvents (Khalifeh 2000). The presence of ionisable groups will affect solubility as shown by the effects of pH on the solubility of ibuprofen. Ibuprofen molecules at pH 7.4 are highly ionised since the pKa of the compound is 4.45. Due to this high degree of ionisation, the molecules are more susceptible to solvation, enabling a higher solubility than at low pH. These results compare reasonably favourably with earlier data reported by Watkinson et al. (1993), where the solubility of ibuprofen was found to be 0.024 $mgml^{-1}$ at pH 2.2, 0.096 $mgml^{-1}$ at pH 5.0 and 3.70 $mgml^{-1}$ at pH 7.0 with water employed as the solvent. At pH 5.0 the solubility did not compare well, possibly due to the different solvent employed.

5.4.4.2. Stability Studies

Basic stability studies were carried out using procaine HCL, ibuprofen, paracetamol and furosemide and these involved incubating the respective drugs in both the control and the spent receiver fluid at 37 °C (Table 5.9). High recovery values, close to 100%, were obtained for these compounds with the exception of temozolomide, indicating satisfactory stability at this temperature over the 48 h study period for the others (Table 5.9). Yet, temozolomide showed instability during the first 24 h, suggesting that this compound would be inappropriate to be used in the subsequent diffusion experiments. Nevertheless, all values for the other compounds were considered within acceptable limits (approximately ± 5% from the target percentage of

recovery), so as to ensure sufficient stability for the period of incubation at 37 °C for a time relevant to the Franz diffusion experiments.

Table 5.9. Stability results of candidate penetrants in 'clean' receiver solution.

Penetrant / receptor fluid	Start. concentration (μgml^{-1})	Time of incubation (h)	% Recovery
temozolomide / distilled water	21.74	0	100.46
		8	80.04
paracetamol / PBS	16.67	48	95.83
furosemide / 40% PEG400	20.00	48	100.23
procaine HCL / PBS : water (20 : 80)	42.55	48	108.03
ibuprofen / PBS pH (7.4)	42.55	48	98.46
ibuprofen (pH 4.2) / 60 ml (0.1 M) citric acid & 40 ml (0.2M), $Na_2 HPO_4$	4.26	48	103.18
ibuprofen (pH 2.6) / 89.1 ml (0.1 M) citric acid & 10.9 ml (0.2 M), $Na_2 HPO_4$	2.17	48	101.68

Table 5.10 shows that when the other four drugs were spiked into the spent receiver fluid, then each demonstrated sufficient stability to be employed as potential penetrants in the skin diffusion studies. The stability of ibuprofen was also investigated under conditions of different pH. At all three pH values investigated, the ibuprofen demonstrated good stability with recoveries approximating 100%, after incubation in both control and spent receiver fluid yield at 37 °C for 48h (Tables 5.9 and 5.10).

Table 5.10. Stability results of compounds incubated for 48 h in spent receiver fluid.

Penetrant / receptor fluid	Start concentration (μgml^{-1})	Time of incubation (h)	% Recovery
paracetamol / PBS	16.67	48	96.40
furosemide / 40% PEG400	20.00	48	97.37
procaine HCL / PBS : water (20 : 80)	42.55	48	105.35
ibuprofen / PBS pH (7.4)	42.55	48	101.78
ibuprofen (pH 4.2) / 60 ml (0.1 M) citric acid & 40 ml (0.2M), $Na_2 HPO_4$	4.26	48	102.38
ibuprofen (pH 2.6) / 89.1 ml (0.1 M) citric acid & 10.9 ml (0.2 M), $Na_2 HPO_4$	2.17	48	106.76

These basic stability studies carried out using procaine HCL, ibuprofen, paracetamol and furosemide involved incubating the respective drugs separately in both the control and the spent receiver fluid at 37 °C. In each case there was a high recovery of intact drug, which showed that these species were stable at this temperature and these media over the 48 h study period. However, temozolomide showed instability during the first 24 h of the study, suggesting that this compound was inappropriate for use in the subsequent permeation experiments. Stability studies were also carried out using ibuprofen solutions in solutions of different pH, specifically at pH 2.4, 4.2 and 7.4 at 37 °C in both the control and the spent receiver fluid. All

solution yielded high recovery values, close to 100%, and showed that these species were stable under conditions representative of those over the projected 48 h study period.

5.4.5. *In Vitro* Permeation Studies – Preliminary Permeation Studies

On the basis of the preliminary permeation studies, ibuprofen, paracetamol, procaine HCl and furosemide were deemed to provide feasible options for use in the Franz Cell diffusion studies. Procaine free base was detected in the receptor compartment after only 1 h, paracetamol after 2-3 h, Ibuprofen after 4-8 h, whilst furosemide required 8-24 h. Following these results, the methodology for the Franz Cell experiments for each compound under investigation was refined and the final methodology defined (Section 5.3.2.7). For both preliminary and actual experiments, epidermal sheets were employed in accordance with the OECD Guidelines 2004a which mimic best the *in vivo* situation. However, while developing the models, broader subgroups (Group A18 and A19) were used due to the limited number of experiments using epidermal sheets in the literature.

5.4.6. *In Vitro* Permeation Studies – Franz Cell Experiments

The concentration of the penetrant in the receptor solution was corrected for previous sample removal. The cumulative amount of penetrant, Q (μgcm^{-2}), which permeated the skin per unit surface area was plotted against time. Table 5.11 presents the cumulative amount of each penetrant together with the corresponding time course of permeation. More information is available in Appendix 24. Suspensions comprising 20% C_{max} were applied to the epidermal membrane so as to ensure a constant thermodynamic activity, without drug depletion occurring during the experiment.

Table 5.11. The cumulative amount of each penetrant and the corresponding time course of permeation.

Compound	Q (μgml^{-1})	Time (h)	Compound	Q (μgml^{-1})	Time (h)
procaine	1688.80	24	ibuprofen (pH 7.4)	592.98	24
procaine	2746.91	28	ibuprofen (pH 7.4)	704.62	28
procaine	3795.58	32	ibuprofen (pH 7.4)	859.34	32
procaine	4660.18	36	ibuprofen (pH 7.4)	1015.76	36
procaine	8280.74	48	ibuprofen (pH 7.4)	1343.31	48
paracetamol	192.77	24	ibuprofen (pH 4.2)	44.10	8
paracetamol	235.87	26	ibuprofen (pH 4.2)	66.00	12
paracetamol	291.36	28	ibuprofen (pH 4.2)	148.51	24
paracetamol	360.41	32	ibuprofen (pH 4.2)	185.32	28
paracetamol	584.27	48	ibuprofen (pH 4.2)	231.35	32
furosemide	15.01	26	ibuprofen (pH 2.6)	68.40	24
furosemide	35.32	28	ibuprofen (pH 2.6)	98.37	28
furosemide	81.80	32	ibuprofen (pH 2.6)	125.63	32
furosemide	131.76	36	ibuprofen (pH 2.6)	172.42	36
furosemide	246.49	48	ibuprofen (pH 2.6)	277.35	48

The mean cumulative amount permeated per unit area (µgcm^{-2}) versus time (h) was constructed for each permeant and is shown in the following figures (Figures 5.3 and 5.4). The linear portion of the plot (five data points) was taken as being the steady state flux (Js) (Al-Saidan 2004). The correlation (R^2) was recorded in each case. It can be seen that the diffusion of furosemide had the shortest lag time, which was estimated from the x-intercept of the linear portion of the profile.

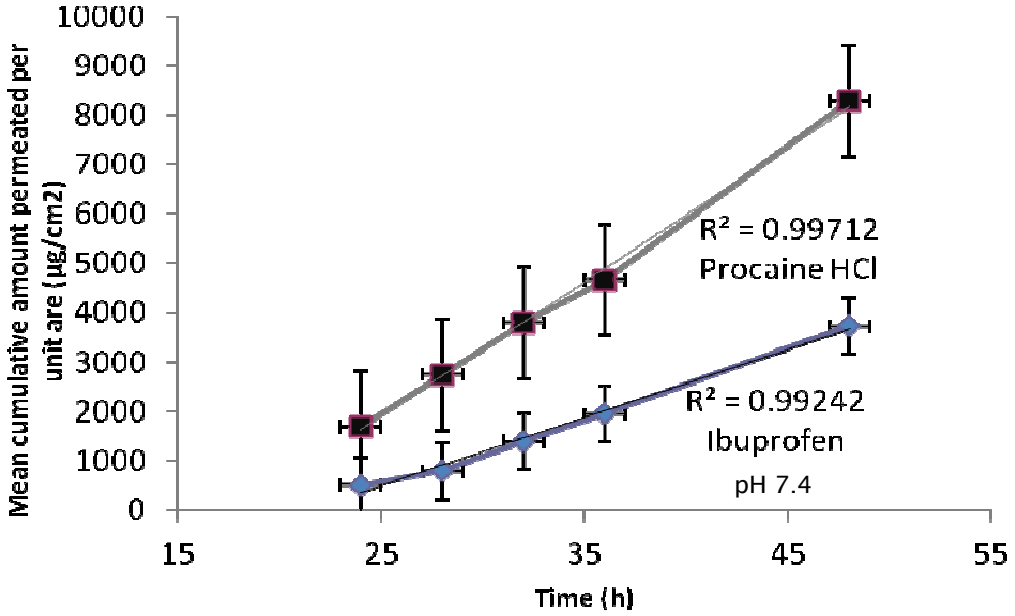


Figure 5.3. Mean (± SD) amount of procaine HCl and ibuprofen (pH 7.4) permeated per unit area (µgcm^{-2}) across human epidermis (n = 6).

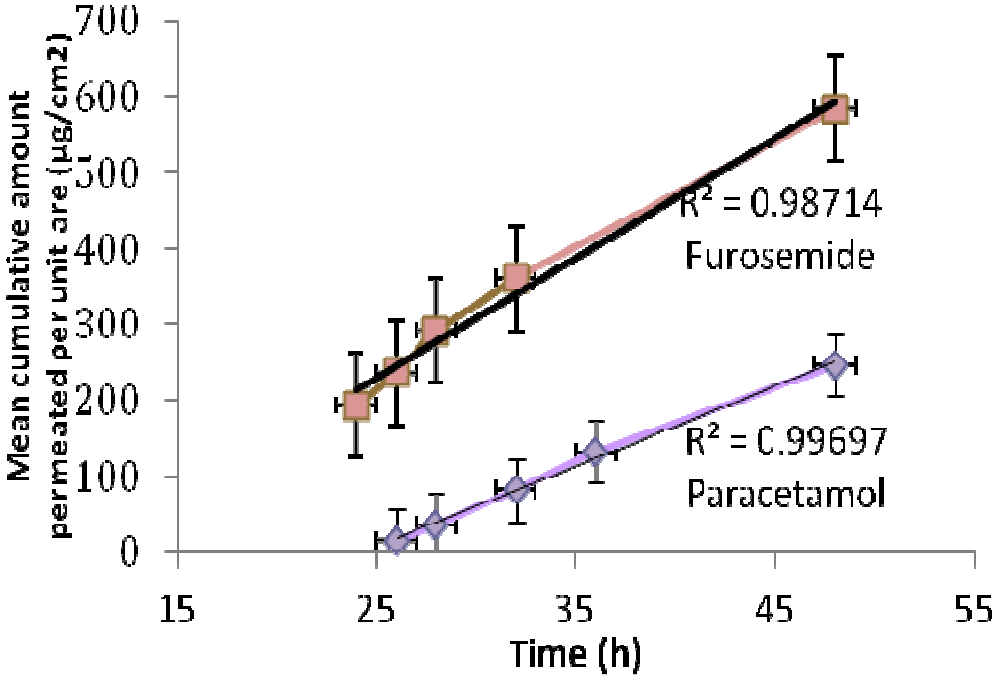


Figure 5.4. Mean (± SD) amount of paracetamol and furosemide permeated per unit area (µgcm^{-2}) across human epidermis (n = 6).

The fluxes of ibuprofen across isolated epidermis were also measured at different pH values. Similar suspensions were applied to the membranes in order to maintain the constant thermodynamic activity of the solution. The mean plots of cumulative amount permeated per unit area (µgcm^{-2}) versus time (h) were constructed for each saturated solution (Figure 5.5).

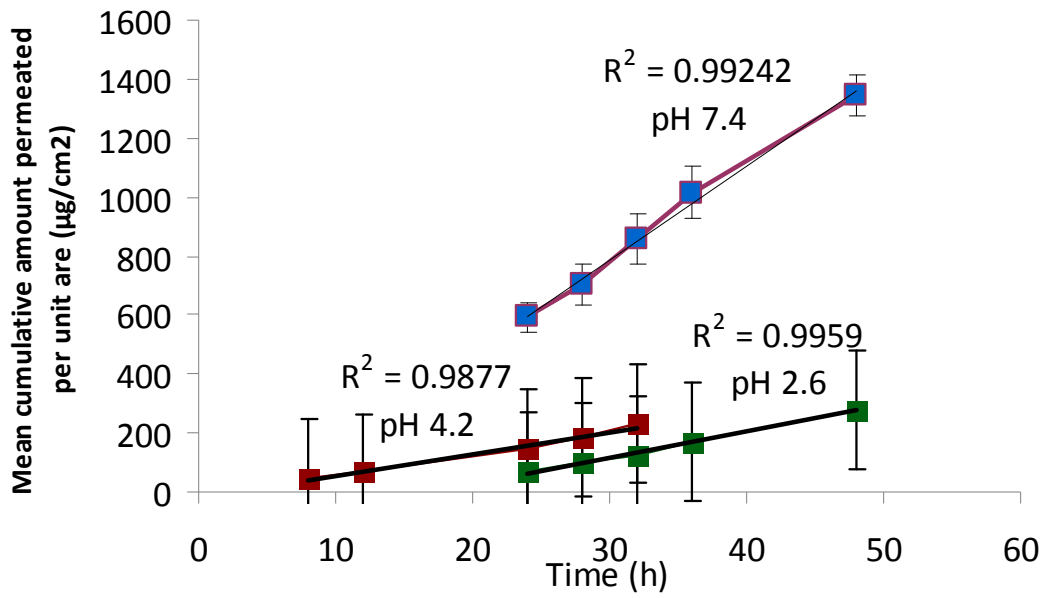


Figure 5.5. Mean (± SD) amount of ibuprofen permeated per unit area (µgcm^{-2}) across human epidermis (n = 6) at pH 7.4, pH 4.2 and pH 2.6.

The rate at which the test compounds permeated human epidermis was found to be in the order of procaine HCl > ibuprofen > paracetamol > furosemide. Furthermore, the rate of ibuprofen diffusion was found to be pH dependent and in the order of pH 7.4 > pH 4.2 > pH 2.6. The flux values obtained experimentally were compared to other values reported previously and with the values predicted from the GP 5f model and the SLN 5f model, developed in the earlier stages of the current study (Table 4.2). Generally, the values obtained experimentally (Table 5.12) correlated well with those obtained from the developed models since the % Mean Absolute Percentage Errors (MAPEs) were generally smaller than 50%. However, this was not the case for the flux of paracetamol and procaine HCl. The values of the flux of paracetamol (Table 5.12) predicted by the models were markedly lower than the experimentally-derived value. Moreover, the values of the flux of procaine HCl predicted by the models were markedly higher than the experimentally-derived value and than the value reported previously in the literature.

The flux of ibuprofen in PBS (pH 7.4), found to be 31.75 µgcm^{-2}h^{-1}, was in close agreement with the values obtained using the GP model, having a % MAPE of 1.45%. The % MAPE is a measure of accuracy, indicating a good agreement of the models in terms of statistical fit. The change in flux of ibuprofen as a function of pH was also well accommodated by the models.

Table 5.12. Flux values (J_{ss}, $\mu gcm^{-2}h^{-1}$).

Name	$J_{lit.}$ ($\mu gcm^{-2}h^{-1}$)	$J_{exp.}$ ($\mu gcm^{-2}h^{-1}$) [b]	$J_{pred}GP$ ($\mu gcm^{-2}h^{-1}$)	% MAPE $J_{pred}GP$	$J_{pred}5f$ ($\mu gcm^{-2}h^{-1}$)	% MAPE $J_{pred}5f$
furosemide	12.90 [i]	10.59 ± 7.22 (n = 4[a]; R^2 = 0.99)	9.18	13.31	5.70	46.17
paracetamol	17.11 [ii]	15.87 ± 3.30 (n = 6; R^2 = 0.98)	0.22	98.63	3.87	75.61
procaine HCL	82.30 [iii]	273.46 ± 4.84 (n = 6; R^2 = 0.99)	1068.90	290.88	98.55	63.96
ibuprofen (pH 7.4)	24.42 [iv]	31.75 ± 5.34 (n = 6; R^2 = 0.99)	31.29	1.44	32.77	3.21
ibuprofen (pH 4.2)	1.31 [iv]	7.59 ± 0.88 (n = 6; R^2 = 0.99)	3.74	50.72	3.92	48.35
ibuprofen (pH 2.6)	1.43 [iv]	6.73 ± 0.168 (n = 6; R^2 = 0.99)	0.30	95.54	0.32	95.24

[a] Due to skin depletion the number of Franz Cells used for this experiment was four.
[b] Values shown as mean ± SD.
[i] Cho et al. 2005
[ii] Sintov et al. 2003
[iii] Jin & Shin 2008
[iv] Hadgraft et al. 2000a

The flux of furosemide was found to be 10.59 $\mu gcm^{-2}h^{-1}$, which was in close agreement with the value obtained by application of the GP model (J_{ss}= 9.176 $\mu gcm^{-2}h^{-1}$), indicating that the GP model predicted well the permeation rate of furosemide through human skin. The predicted flux values in all cases were calculated from the corresponding predicted K_p values. Furthermore, the experimental value obtained in the only known previous study for the diffusion of furosemide across a synthetic membrane (Cho et al. 2005) was in reasonable agreement with that obtained in the current study using human skin. The measured flux of furosemide through the EVA copolymer membranes was 12.90 $\mu gcm^{-2}h^{-1}$ (Cho et al. 2005), which is comparable, although higher, to the release rate obtained experimentally through human skin. The flux of ibuprofen obtained experimentally at pH 7.4 was found to be 31.75 $\mu gcm^{-2}h^{-1}$, a value which compares favourably to values predicted by the GP model and the 5f model (Table 5.12). Thus, all models appeared to accommodate the permeation of ibuprofen through human skin under conditions that are broadly pH neutral. Indeed, the flux of ibuprofen across human epidermis was also in agreement with those reported previously from 0.1 to 0.4 M disodium hydrogen phosphate saturated solutions, which range from 35.4 to 332.0 $\mu gcm^{-2}h^{-1}$ respectively. The composition of the vehicle in which ibuprofen is presented to the membrane (and whether buffer capacity of the media is exceeded) could influence the resultant flux, given that this is dependent upon the state of ionisation of ibuprofen. Ibuprofen has been reported to be capable of developing a self-permeation enhancement capacity, leading to a disruption of the stratum corneum barrier, since in its ionised form, ibuprofen can act as anionic surfactant. Surfactants are known to act as chemical penetration enhancers for transdermal delivery of drugs (Section 1.5.2). Ibuprofen has been proven to have a low surface tension, suggesting lower drug / skin interfacial tension, which in turn could have improved the contact between the drug and skin leading to self-permeation enhancement of the drug (Al-Saidan et al. 2004).

Despite the value obtained for the flux of paracetamol comparing favourably with a previously reported value (Sintov et al. 2003), both these values correlated poorly with the predicted values derived using either of the two models. The poor

correlation of paracetamol fluxes could be due to the ionisation of paracetamol. The latter is an amphoteric drug with both acid- and amino-groups and therefore depending upon the pH, paracetamol can act as a cation, anion or as zwitterion. Use of the Henderson-Hasselbalch equation indicates that at pH 7.73, paracetamol is only 2% ionised. Depending on the pH of the vehicle and the pKa of a compound, an equilibrium mixture of ionised and unionised species would be present in the immediate vicinity of the skin. To properly control the rate at which such electrolytes permeate through human skin, it is necessary to determine the permeability of both forms of the drug. Generally, it is the non-ionised forms that diffuse more readily through the lipoidal membranes. However, at pH values near neutrality, the other compounds employed here are fully ionised in solution (Table 5.13). Since ibuprofen and furosemide are fully ionised, the high correlation of the experimental values with those predicted by the models suggests that the latter accommodated the ionised species. This may be due to the fact that all predicted models were developed from data, the majority of which were determined under various ionisation environments and not under controlled pH conditions. Hence, the consideration of pH for ionised drugs may not have been satisfactorily accommodated in the model development.

The flux of procaine HCl through human skin was higher than that obtained previously (Table 5.12) but was five times smaller than those derived from the GP model and almost three times higher than that predicted via the 5f model. However, the previously reported data make reference to procaine, rather than the hydrochloride salt, and pH control could again be in issue in appreciating, which is the diffusing species.

A possible reason for discrepancies between experimental data obtained here and data derived in some of the models is that it is conceivable that, since the saturated solutions were applied as suspensions, some supersaturation of the solution could have occurred over the 48 h of the study. In a supersaturated system, the drug is presented in solution at a level greater than its saturated solubility, resulting in a thermodynamic activity higher than would normally be attained and these result in a higher than predicted skin permeability rate. Supersaturation is used as a method of enhancing permeation which theoretically has no effect upon the barrier properties of the skin and increases the concentration of the drug in the application vehicle past the saturation point to create a supersaturated solution. Supersaturation is attained when a compound is solubilised in a vehicle at a concentration greater than the saturated equilibrium solubility (defined as a thermodynamic activity of one). The increase in drug concentration above equilibrium in a vehicle increases its thermodynamic activity, which in turn proportionately increases the rate at which the drug can permeate through the skin, according to the Higuchi equation. A linear correlation between degree of saturation and flux has been demonstrated previously to exist and this relationship extends into the supersaturation range of solutions (Twist & Zatz 1988; Iervolino et al. 2001; Moser et al. 2001b).

Table 5.13. The percentage of compounds that are ionised at the pH values at which the solutions were applied to the skin in these studies.

Name	pKa	pH	% ionisation
furosemide	3.90	7.00	100.00
ibuprofen	4.45	7.40	100.00
ibuprofen	4.45	4.20	36.00
ibuprofen	4.45	2.60	1.00
paracetamol	9.38	7.73	2.00
procaine HCL	8.90	7.00	93.00

The data presented in Table 5.14 show that procaine HCL has a greater flux value when this is predicted according to GP model in comparison to the equivalent values obtained using the Potts and Guy (1992) and revised Robinson (1995) models. Also, the flux values estimated for ibuprofen from Potts and Guy (1992) and revised Robinson (1995) equations were higher than the values obtained experimentally and via the other predictive models (Tables 5.11 and 5.14). These inconsistencies might be due to inherent experimental errors or most probably due to the fact that the Potts and Guy (1992) and revised Robinson (1995) models are linear. Nonlinear modelling might provide a prediction for percutaneous absorption for molecules with a wide range of log P values. Finally, it is worth noting that although the 5f model is a linear model, it predicts better the flux of both ibuprofen and procaine HCl compared to the Potts and Guy (1992) and revised Robinson (1995) models, suggesting that the inclusion of further parameters such as hydrogen bonding and Fedors' solubility provides results closer to those obtained experimentally.

Table 5.14. Permeability coefficient predictions of the models under investigation.

Model	Name	Log P	MW	SP	Ha	Hd	K_p (pred) (cmh^{-1})	Conc. x 10^5 (μgml^{-1})	Flux ($\mu gcm^{-2}h^{-1}$)
Gaussian Process	procaine HCL	-0.84	272.78	10.58	3	1	0.00016	66.44	1068.94
	ibuprofen	3.79	206.28	10.21	1	1	0.0051	0.25	126.85
	furosemide	2.32	330.75	19.07	3	3	0.00069	0.13	9.18
	paracetamol	0.27	151.16	13.28	2	2	5.2×10^{-5}	0.04	0.22
Potts and Guy (1992)	ibuprofen	3.97	206.28	N/A	N/A	N/A	0.073	0.25	1786.84
	procaine HCL	-0.84	272.78	N/A	N/A	N/A	1.09E-05	66.44	72.80
	furosemide	2.32	330.75	N/A	N/A	N/A	0.00085	0.13	11.22
	paracetamol	0.27	151.16	N/A	N/A	N/A	0.00037	0.04	1.56
5ff	ibuprofen	3.79	206.28	10.21	1	1	0.0054	0.25	132.99
	paracetamol	0.27	151.16	13.28	2	2	0.00077	0.42	3.23
	furosemide	2.32	330.75	19.07	3	3	0.00036	0.13	4.80
	procaine HCL	-0.84	272.78	10.58	3	1	0.00012	66.44	821.27
revised Robinson (1995)	ibuprofen	3.97	206.28	N/A	N/A	N/A	0.028	0.25	698.29
	furosemide	2.32	330.75	N/A	N/A	N/A	0.00069	0.13	9.20
	paracetamol	0.27	151.16	N/A	N/A	N/A	0.00045	0.04	1.89
	procaine HCL	-0.84	272.78	N/A	N/A	N/A	2.55E-05	66.44	169.37

The flux values of ibuprofen and furosemide determined from either the GP or the 5f models, agreed well with the corresponding values obtained experimentally, given the small % MAPE associated with these compounds (Table 5.12). Procaine HCl diffused at a rate smaller than predicted using the models' rates and paracetamol diffused at a much higher rate than was predicted from the GP model, although as stated above the latter could be possibly due to the relatively small degree of paracetamol ionisation at pH 7.7 (Table 5.12). The K_p values that have been and are still now being employed in

QSPR development were determined before the existence of the OECD guidelines and are typically drawn from sources where experiments were not conducted under standardised conditions, where the compound might be unionised or only partially ionised. Consequently, in order to investigate further the issue of the ionisation effect, the flux values of ibuprofen were determined from solutions controlled at three different pH values.

5.4.7. The Effects of pH on Diffusion and the Use of log D in Model Development

The pH was calculated for a variety of studies and the relevant log D values were determined (Section 1.4.2.2). The majority of these studies reported experiments in non-buffered solutions. Consequently, Equation 3.10 was not used for the validation stage of the current chapter. Instead, Equation 3.12 was used, based on log D values reported by Avdeef (2003). As already discussed in detail in Chapter 3, these values were critically selected to represent high quality results (Appendix 22). Many constants were also personally determined by Avdeef (2003) (Section 3.4.3.1). Additionally, log D values were also determined computationally, by using pKa, log P and log P^{ion}. The predicted permeability coefficients were calculated in all pH environments. Table 5.15 shows the permeability coefficients determined experimentally at pH 7.4, 4.2 and 2.6 and compared to those predicted using the model.

Table 5.15. Permeability values (log K_p, cmh^{-1}) determined in different pH environments and as predicted by the models using log D values.

Name	Log K_p (pred) (2f model)	Log K_p (pred) (5f model)	Log K_p (exp)
ibuprofen (pH 7.4)	-2.56	-2.58	-2.28
ibuprofen (pH 4.2)	-2.16	-2.69	-1.98
ibuprofen (pH 2.6)	-2.61	-3.43	-0.94

The flux of ibuprofen at pH 7.4 was found to be 31.75 $\mu gcm^{-2}h^{-1}$ (Table 5.11), which was in a close agreement with the values obtained from using the GP model. Within a low pH environment, ibuprofen exists in its unionised state and hence, a high flux value would be expected, whereas in a solution of pH 4.2, its flux value might be expected to be higher than that predicted at pH 7.4. However, it was found that as the degree of ionisation was increased from a pH of 2.4 up to 7.4, the flux also increased (Table 5.11). This was due to the high solubility values obtained when the molecule was ionised. As flux is the product of the permeability coefficient and the saturated concentration, it also depends on the concentration of the saturated solution. The permeability coefficient, being a constant, would be expected to be higher at lower pH values when the non-ionised form predominates. Indeed, the permeability coefficient of ibuprofen was found to be 0.005 cmh^{-1}, 0.01 cmh^{-1} and 0.114 cmh^{-1} for pH 7.4, 4.2 and 2.4 suspensions respectively, showing that as the ionisation degree decreased, so the

permeability of ibuprofen increased. The permeability coefficient at lower pH was dominated by unionised species, whereas at higher pH it was dominated by the ionised species.

The highest permeability coefficient was determined at pH 2.4, when 1% of ibuprofen was ionised (pKa 4.45) (Avdeef 2003). It is interesting to note that the steady-state flux of ibuprofen was greater at higher pH, whereas its permeability coefficient was higher at lower pH when the fraction of unionised species was greater. This suggests that at higher pH the lower permeability of the ionised species was more than compensated for by the increased solubility, which is consistent with the findings of other studies (Benson et al. 2004). Most of the data used for the determination of all models were not derived under specific pH environments and therefore the ionisation effect is not considered within such datasets.

Table 5.12 shows that there was a good agreement between the permeability coefficients determined experimentally at pH 7.4 and 4.2 and the predicted permeability coefficients calculated from both ionisation models (2f and 5f). On the other hand, at pH 2.6, the predicted value did not compare well with the one obtained experimentally. The flux measured at pH 2.6, when compared with the corresponding predicted one, showed an extremely high mean absolute percentage error, suggesting that there was a large difference between the experimental and the predicted values. This might be due to the fact that at such a low pH the solubility of the drug is small, providing only a relatively small flux and, thus, a high K_p value, too high for the model to be able to predict.

5.5. CONCLUSION

Validation is one of the most important processes in data mining, because it actually measures the accuracy of the models developed. Validating already developed models gives confidence to research workers when using them to better understand the potential rates of molecule penetration across the skin. The evaluation results have shown that the predicted permeability coefficient values calculated from the GP model were found to be in a good agreement with those that were experimentally derived. According to the % MAPE, out of the six measurements, three were found to be in good agreement with the GP predictions. Procaine HCl, paracetamol and ibuprofen (pH 2.6) were not found to be in good agreement with the GP predictions. This was due to the fact that for paracetamol the % ionisation was found to be 2, indicating that the GP model works better with the uncontrolled (in terms of pH) data. For ibuprofen (pH 2.6), the solubility was too small and provided a very high K_p value, too large for the model to handle. Therefore, due to their nature, these two compounds were not suitable for GP predictions. In conclusion, out of the six compounds measured, only four were suitable candidates and out of these four, three were found to be in good agreement with the GP predictions, raising the prediction percentage to 83.3%. In order to further support this statement, more compounds need to be used for the validation of the GP models. Unfortunately, due to time restrictions this was not possible for the purpose of this thesis and, for this reason more measurements have been suggested as future work in Chapter 6. Additionally, the GP model was shown to be an accurate nonlinear skin

permeability predictor, since the variability present in the developed model compares favourably to the level of variability expected in the experimental data. Nonlinear models, such as the GP model, do appear to provide a better prediction compared to linear models and they incorporate a wide range of lipophilicity. They appear to accommodate the conclusions of Flynn (1990) that very hydrophilic and very hydrophobic compounds were represented by different mathematical relationships, suggesting, among other things, nonlinearity to transdermal drug diffusion.

However, even though the GP model has statistically outperformed other methods, such as QSPRs, it has certain limitations, too. First, due to the restricted number of controlled experiments available in the literature, the model was developed with the application of a small volume of data both in the training and in the test sets. The size of the datasets appears to influence the quality of the model (Moss et al. 2011). Second and most importantly, the ionisation effect has not been taken into consideration as the log D values are omitted from the model's development process. The transport and uptake of ionisable compounds within biological systems has been difficult to predict and they are often classified as outliers in the common predictive linear models. As a result, the developed GP model provides little information with respect to the ionisation effect. This problem was partially resolved with the development of the ionisation equation described earlier (Equation 3.12), although its linear nature is not that descriptive. In Chapter 4, it was clearly shown that there exist more complex nonlinear patterns within the data. Therefore, these significant limitations can encourage further research into extending the GP model by incorporating other parameters that could possibly take into account the effects of pH, such as replacing the log P with the log D value.

Chapter Six

General Discussion

The ability to predict accurately the dermal permeation of a chemical is important for the development of new therapeutic formulations in transdermal drug delivery, for the assessment of potential risks of environmental chemicals and also for agents used in the cosmetics industry. There are a large number of studies, both experimentally- and theoretically-based, investigating skin permeability. The experimental measurement of skin permeability is a time-consuming and difficult process and, when the great numbers of chemicals, which may come into contact with the skin are taken into account, it is also costly. As a consequence, there has been a great interest over the past years to efficiently 'predict' the ability of a compound to cross the skin from its physicochemical characteristics; therefore, a number of mathematical models have been reported. These models can be classified into empirical and mechanistic models. Most models are empirically derived and are based on experimental data, with skin permeability linearly correlated to the physicochemical properties and / or molecular structure parameters of the chemical compounds. A multi-linear regression method is often used to fit available experimental data and such empirical models are often referred to as linear quantitative structure-property relationships (QSPRs) (Lian et al. 2008). Many of the QSPR models that have been developed relate skin permeability to the physicochemical properties of the solutes (Barratt 1995b), while others use molecular structure properties. Several empirical models were proposed to relate skin permeability to the octanol / water partition coefficient and to the molecular weight (MW) of molecules (Flynn 1990; Kalia et al. 1998). QSPR techniques have been appearing in the literature for over a century, but they do not completely eliminate the need for chemical synthesis or experimental validation. Nevertheless, the successful application of such models can realise a marked reduction in the number of molecules requiring synthesis and validation.

The current study has reviewed the development of QSPRs for the absorption of chemicals through the skin, has identified the challenges and limitations in using those as predictive tools and has defined the way that this technology can be exploited for future research. In terms of skin permeability data with respect to QSPR analysis, it is true that the science has not been developed significantly since the publication in 1990 of what is now universally-known as the Flynn dataset (Flynn 1990). The Flynn dataset is a compilation of skin permeability coefficients (K_p) for 94 compounds with a significant range of physicochemical properties. The data were assembled from at least 15 different publications which lacked consistency in the experimental protocols. Many models have been developed based on the Flynn dataset, but the most frequently encountered was created by Potts and Guy (1992). Since the publication of the Flynn dataset, there have been a number of efforts to expand it in terms of the number of chemicals and the coverage of the compounds. A larger dataset of 114 skin permeability values was prepared by Kirchner et al. (1997) using the Flynn (1990) dataset, together with additional data from regulatory reports from Health Canada. However, data for 56 of the 63 additional chemicals were not experimentally derived (Poda et al. 2001; Frasch & Landsittel 2002; Walker & Comber 2003). Apparently not appreciating this, Cronin et al. (1999) analysed the Kirchner et al. (1997) dataset. Nevertheless, the performance of the revised model was improved over that of the Potts and Guy (1992) model ($R^2 = 0.86$ versus $R^2 = 0.67$) (Poda et al. 2001). In 2002, Patel et al. (2002a) collected and analysed a dataset of 186 permeability coefficients for 158 structurally-diverse compounds from human *in vitro* skin data from Flynn (1990) and Wilschut et al. (1995), providing a good statistical fit. It was appreciated that the hydrogen bonding capability of a molecule affects its ability to permeate the skin (Patel et

al. 2002a). These research workers also found molecular weight to be a better predictive input than molecular volume. A number of further analyses have been carried out, but most continue to utilise the Flynn dataset as their basis (Lien & Gao 1995; Barratt 1995a; Potts and Guy 1995; Abraham et al. 1995; Hostýnek & Magee 1997; Abraham et al. 1999; Dearden et al. 2000).

Most early modelling efforts utilised QSPR models. However, since most thermophysical properties have nonlinear relationships with chemical structure, traditional linear algorithms often result in inferior QSPR models. Consequently, a small number of nonlinear models, accounting for all the structural features of importance to skin permeation and avoiding the problem of an over-reliance on linear models, was developed (Pannier et al. 2003; Neely et al. 2009). In any case, both linear and nonlinear models currently available in the literature have identified challenges and demonstrated limitations.

The advantages of QSPRs rest on the fact that they provide an algorithm capable of predicting the chosen activity for untested compounds providing the chemical structure is known. This has resulted in a possible means of rationalising product development since the properties of potential compounds can, in theory, be determined prior to their synthesis. This has led to a more efficient product-discovery process, reducing costs and animal usage (Dearden & Cronin 2005). Another advantage of QSPR development was the insight provided into the mechanisms of actions. QSPRs are also important in the assembly of risk assessment information as required by Regulatory Agencies. It was envisaged that QSPRs could be used by these bodies for filling data gaps, for prioritising chemicals for testing and also for classifying and labelling (Cronin et al. 2003; Cronin et al. 2003). Additionally, the US Environmental Protection Agency (EPA) provided guidelines for dermal risk assessment in 1992 (EPA 1992) and advocated the use of a computational equation for estimating K_p values whenever experimental data are unavailable (Mitragotri 2011). Apart from the advantages presented above, there are important limitations when using QSPRs for model development. First, the literature contains a wide range of conflicting experimental protocols for the determination of percutaneous absorption. Such interlaboratory variation results in a lack of consistency in the data introduced into the database and this ultimately translates into variability or error in the QSPRs developed. This variability can be manifested by a lesser statistical fit of the data to the resultant model. Ideally, in order to assess the relationship between different methods, the relative permeabilities of the same compounds should be assessed. However, for some compounds, it was found that more than one source of the K_p value for the same chemical was available in the literature. Although previous researchers (Potts & Guy 1992; Monteiro-Riviere et al. 2005) have indicated that the scale of variance might be acceptable and within the expected range of variability in skin delivery experiments (Moss et al. 2002), such variance decreases the statistical validity and accuracy of all developed models.

Another problem that may be considered as a limitation whilst developing QSPRs is the tendency to over-fit data. When developing a model, it is tempting to try to maximise the data fit by deleting outliers. Modellers tend to eliminate certain substances or classes of substances from databases in order to increase the resulting statistical fit (Fitzpatrick et al. 2004), even when it is possible to argue that certain substances or classes of substances can be expected to be anomalous. However, it is not satisfactory to remove data from the pool primarily because their behaviour does not comply with a standard model.

Furthermore, the selection of optimal physicochemical parameters is of great importance, since the rate and amount of percutaneous absorption of a compound greatly depend on both the physiological characteristics of the skin (e.g. skin thickness, hydration and temperature) and on the physicochemical nature of the compound (e.g. hydrophobicity, polarity, physical state, water solubility and molecular mass or size). In order for the passive diffusion process to be well-described, the correct descriptors of the physicochemical and / or structural properties of the compounds should be identified and selected. QSPRs should accommodate compounds with as broad a range of physicochemical parameters as possible. Normally, most QSPR models suggest that log P and molecular weight (MW) are the most significant descriptors of permeability. On the other hand, others (Potts & Guy 1995; Pugh et al. 1996) have shown that other parameters, particularly hydrogen bonding, are of importance (Geinoz et al. 2004; Sun et al. 2011). It is recognised that compounds with greater hydrophobicity are generally absorbed more readily by the skin than the less hydrophobic and that dermal absorption generally increases as log P increases from 1 to 3.5. Although highly lipophilic substances (log P > 5) can pass easily through the stratum corneum, they are generally too water-insoluble to pass through the remaining sublayers and enter the bloodstream. Consequently, there was a need to develop more descriptive models based on specific log P ranges rather than the whole set of values. Additionally, molecular size is an important factor in membrane permeation (Berner & Cooper 1984; Cussler 1997). There is good evidence that permeation and maximum flux decrease exponentially with MW (Kasting et al. 1987; Potts & Guy 1992; Magnusson et al. 2004). Thus, the extent of absorption of compounds with a MW over 500 Da through normal human skin is low (Bos & Meinardi 2000). Lam et al. (2010) suggested that certain physicochemical parameters were effectively interchangeable or possibly colinear and that removing or adding certain physicochemical descriptors to the model did not always affect its statistical quality or its ability to accurately predict permeability. Therefore, during the selection process of the most suitable parameters to be employed for permeability predictions, a balance between the number of the descriptors and the actual significance of each descriptor has to be considered.

Additionally, the majority of developed models have demonstrated a linear relationship between hydrophobicity and skin permeation (where permeation may be described as either flux or permeability coefficient) (Scheuplein & Blank 1971; Roberts et al. 1977a). Such linear relationships were regarded as integral to the statistical models since such a correlation is mathematically simple and the treatment readily transparent (Aptula et al. 2002). A disadvantage of these models is that they are adversely affected by colinearity between independent variables (e.g. log P_{ow} and MW). The use of colinear descriptors is undesirable, for two reasons. First, two highly colinear descriptors are effectively contributing the same information twice and, thus, add nothing to mechanistic interpretation of a QSPR; in fact, they can detract from it. Second, it is known that the use of colinear descriptors can have adverse effects on the statistical analysis, for example by causing instability in the regression coefficients (Cronin et al. 2003). Accordingly, regression analysis may not provide a suitable means for developing QSPRs; and it is unclear whether the apparent requirement for linearity is appropriate when modelling both highly hydrophilic and hydrophobic molecules. Therefore, new models accommodating more of the structural features of importance to skin permeation and avoiding over-reliance on linear models may be required. On the other hand, the nonlinear models currently

available in literature have been developed using the Fuzzy Logic and Artificial Neural Network (ANN) methods. Even though both are suitable methods for identifying and extracting both the linear and nonlinear effects of chosen descriptors on skin permeability, they tend to be more complicated in terms of interpreting and understanding the final results (Chen et al. 2007; Pannier et al. 2003).

One of the factors often ignored in skin absorption studies and specifically in the prediction of skin permeability is that many potential permeants are weak acids or bases and, thus, may be ionised at specific pH. When the penetrating species exist in both ionised and unionised forms, it is likely to be the unionised that will permeate faster through the lipid regions while the ionised might penetrate more slowly through the aqueous regions. Ionisation would be expected to be a major factor in determining skin permeation, even if it has rarely been incorporated explicitly into predictive models. Acidic and basic solutes will have various degrees of ionisation depending on the vehicle pH. Fitzpatrick et al. (2004) reanalysed the dataset assembled by Patel et al. (2002a) and reported problems associated with the variability of the K_p data. The earlier workers also suggested that there were problems associated with using partition coefficient values for ionisable compounds since pH adjustment is required to ensure that compounds were in the unionised state (Fitzpatrick et al. 2004), although they may be determined in accordance with recommended guidelines (e.g. OECD Test Guideline 117; OECD 2004d).

Many QSPR analyses available in the literature still contain errors, despite numerous recommendations in print and a set of five requirements detailed in the OECD Principles for the Validation of (Q)SARs (2004) and published with the aim to avoid such errors. Most of the errors relate mainly to the quality of the data involved and to the lack of appropriate measures to assess goodness of fit, robustness and predictivity. The latter parameter relates to the statistical aspects of QSPR modelling and to the number and quality of the descriptors involved. It is important that the errors of past QSPRs are recognised and that new datasets are assembled to ensure that new models are developed with better predictive ability.

A multitude of molecular descriptors were available in the literature (Todeschini et al. 2000). Lam et al. (2010) have argued that certain of these descriptors were effectively interchangeable or possibly colinear and that removing or adding them to the models did not affect their ability to predict skin permeability. Hence, the current work employed lipophilicity and molecular weight, together with other methods previously used (Pugh et al. 1996; Sun et al. 2011). Five physicochemical descriptors were examined in total: log P, MW, the number of hydrogen bond donor (Hd) and acceptor (Ha) groups and the solubility parameter (SP), the latter being defined by Fedors (1979). Fedors' group contribution method (1974) was selected since only knowledge of drug structure is needed to calculate SP and values for large numbers of functional groups are available. However, the aim in model development was to utilise the minimum number of parameters used in any equation under development whilst obtaining a good statistical fit. In adopting such an approach, it was hoped that the problems reported earlier (Chen et al. 2010), associated with avoiding the use of multiple parameters, would be overcome. Furthermore, values taken from literature sources were carefully checked, ensuring accuracy of the databases generated for each skin or membrane type. It was also recognised that past, measured or derived, property values were obtained from different sources and this might also have introduced variation to the resulting models. Consequently, multiple QSPR software packages were used to provide descriptors, aiming to assure model stability.

A further potential difficulty with reported transdermal absorption data relates to the large variation in the experimental methodology employed in their generation. Several of these published models of skin permeation were based on data gleaned from multiple sources using inconsistent experimental protocols (Cronin et al. 2003; Cronin et al. 2006). Interlaboratory comparative studies should include appropriate internal and external quality controls, i.e. the use of a validated experimental technique mimicking as closely as possible the *in vivo* environment. The construction of databases containing measured and well-defined skin absorption data is a key first step in the development of QSPRs and this also provides a basis for research aimed at improving the understanding of the dermal absorption process of chemicals. Several studies have examined the inter- and intraindividual differences in permeability (Akomeah et al. 2007a; Lee et al. 1994). Assessment of the quality of a model is critically dependent upon knowledge of the possible experimental variability associated with the data, since the model performance is unlikely to exceed this variability. Exclusion of the variability of skin-related factors results in a smaller experimental deviation. Most of the previously developed models are based on data generated from either aqueous or ethanolic solutions, where each penetrant is presented at its saturated solubility or a fraction of its saturated solubility.

Large internally-consistent datasets are hard to obtain, because skin permeation studies are labour intensive. Nevertheless, effort was made in the current study to construct a large database of consistent data. Based on this dataset previous models were re-evaluated and new quantitative permeability models were developed. In order to evaluate the predictive capability of various mathematical models, two large databases, Database B and Database C, were employed. In Database B, all data were derived from sources published in the literature but the membranes employed during the conduct of the experiments were identified. Database B, as shown in Appendix 2, consisted of 167 compounds. Specifically, there were 70 compounds in the human skin dataset, 43 compounds in the mouse skin dataset, 36 compounds in the rat skin dataset and 18 compounds in the silicone membrane dataset. Database B included data from the Flynn (1990) dataset together with other published data. A larger database, Database C (Appendix 3) containing 310 compounds was developed by combining all the data existing in the EDETOX database with the data published by Wilshut et al. (1995) and Patel et al. (2002a) and other *in vitro* data derived from other separate sources. The difference between Database C and Database B is that the former contains compounds with corresponding permeability coefficients derived under specific experimental conditions, i.e. via specific experiments obtained using detailed protocols. A minimum set of criteria were required to describe all experimental protocols such as type of skin, vehicle, dose, area of exposure, exposure time, receptor fluid, diffusion cell, method of membrane preparation, analysis, study length and temperature. Should replicate values be included when identical structures are present in the training set, these may unduly influence the resulting algorithm. Accordingly, effort was required to prepare a clean, replicate-free dataset at the beginning of QSPR studies. Database C, comprising 310 compounds (600 K_p values, Appendix 3) was then divided into smaller datasets according to common experimental similarities. Different QSPRs were developed for each specific group and it was found that under different experimental conditions the resulting QSPRs differed in terms of statistical fit. This led to the conclusion that the statistical fit of different models was dependent on the experimental conditions employed and therefore confirmed that data should be grouped according to common experimental conditions

and then analysed and interpreted separately. Group A1 (Appendix 5) was designated as the most 'ideal' dataset although it was deemed that it was not as descriptive as it should be due to its small size. For this reason, the human Group A17 (145 compounds, Appendix 5) was considered as the best alternative to be employed in the model development process in terms of experimental quality and number of compounds involved. However, three compounds were excluded from the dataset due to the inability of calculating specific physicochemical properties as Fedors' solubility, melting point and the numbers of hydrogen bond donor and acceptor groups; thus, Group A18 resulted (142 compounds, Appendix 5).

In order to examine the boundaries of the models available in the literature, the most frequently cited mathematical models were selected. Four QSPRs were evaluated based on Database B (Evaluation B) as shown in Appendices 2 and 11-14 and five QSPRs (the previous four together with the Barratt 1995b model) were evaluated based on Database C (Evaluation C) as shown in Appendices 3 and 15-19. It was found that in both evaluations and in all models, the resulting regression coefficients, obtained when the new predicted K_p values were compared to those obtained experimentally, decreased. As the number and variety of compounds in both databases increased, the 'goodness of fit' declined. In Evaluation B, the dataset did not contain any outliers. For Database C, only those permeability coefficient values that were derived under specific experimental conditions were used. There were no restrictions in terms of the chemical structures involved, resulting in a wide range of data. Such variation in physicochemical parameters might have resulted in a decrease in the statistical fit. Even though Database C became cleaner, since it consisted of permeability values derived under specific experimental conditions, and even though it was consolidated, the statistical validity of the analyses conducted within it decreased. This was due to the inclusion of a variety of compounds in the data.

Extrapolating a model substantially beyond its boundaries (i.e. outside the range of data input to the model) cannot be recommended and this provides a clear limitation to its applicability. Even if a model is within these boundaries, it may still be difficult to be uniformly accurate if it is developed from a database that is poorly or unevenly distributed, for example, a database exhibiting a high degree of redundancy in its data. In real life, variability within specific experimental parameters (such as temperature and site of application) is expected, but not within all of them. In Chapter 4, the Gaussian model developed did not incorporate all experimental parameters but was rather focused on human skin data. This was mainly due to the limited size of available data in the literature.

By manually manipulating the datasets derived from different experimental conditions, novel linear QSPRs were developed. These are all summarised in Table 6.1. The ionisation effect, lipophilicity effect, together with the effect that the majority of the experimental conditions have on the K_p measurements, were incorporated into the new linearly-developed QSPRs. Except from the ionisation model (Equation 3.12), all models employed log P values as an indicator of lipophilicity. In contrast, the ionisation equation used the distribution coefficient instead, since it refers to a collection of species which varies dependent on pH. The majority of the log D values employed were gathered from the literature whilst others were computationally derived (Avdeef 2003). Even though these originated from cleaned data, when compared with past QSPRs, they were shown to fit less well in terms of statistical validity. This was mainly due to the fact that, by classifying compounds into specific subsets, a smaller number of compounds of

high structural diversity were used for their development (Table 3.10). The new linearly developed models, apart from being constructed from robust datasets, presented limitations, which were due to the small number of data employed for their development. While a particular dataset is quite large in size, an uneven distribution of data may affect the model produced; hence, the size of the dataset may only be relevant when the compounds included have as wide a range of physicochemical properties as possible. Such an understanding of both the size and distribution of the data used to develop models might impact on the quality of the analysis. In order to compare two of the models, the size of the database should be the same. This is the reason that only two of the four fit (Table 6.1); furthermore, even when the size is the same, there are other parameters – such as additional physicochemical inputs – which can change results. Potts & Guy (1992) based on the Flynn dataset, Barratt (1995b) based on the Flynn dataset again, Cronin et al. (1999) on the Flynn dataset and Health Canada data and revised Robinson (1995) were determined using poor quality data in most cases. Therefore, they cannot be compared to the ones developed for the purpose of this thesis as the latter were developed from carefully reviewed and controlled data.

Additionally, even though the newly-developed linear models incorporate important factors such as the pH effect (Equation 3.12), they fail to predict a wide range of permeability (in terms of physicochemical properties) due to their linearity. For example, very low or very high log P values were poorly modelled and their absorption remains quite poorly understood. As a result, it was perceived that there was a need to develop non-linear models based on Gaussian process (GP).

Table 6.1. Linear and nonlinear QSPRs (comprising a combination of Tables 3.10 and 4.2).

Models	Dataset employed	N	R^2	Linearity
Potts and Guy (1992)	Flynn (1990)	93	0.67	linear
Potts and Guy (1992)	Group A19	149	0.18	linear
Barratt (1995b)	Flynn (1990)	60	0.90	linear
Cronin et al. (1999)	Flynn (1990) + Health Canada (WHO 2006)	107	0.86	linear
revised Robinson (1995)	Wilshut et al. (1995)	99	0.51	linear
Moss and Cronin (2002)	Group A19	149	0.21	linear
Group A1 QSPR	'Ideal experimental conditions'	11	0.61	linear
Static Cell QSPR	Group A12	25	0.43	linear
Flow-through Cell QSPR	Group A11	25	0.24	linear
Temperature 32 °C	Group A9	24	0.41	linear
Temperature 37 °C	Group A10	24	0.39	linear
Rec. fluid QSPR – buffer	Group A13	64	0.34	linear
Rec. fluid QSPR – buffer & water	Group A15	79	0.37	linear
Ionisation QSPR (1)	Group A20	20	0.52	linear
Ionisation QSPR (2)	Avdeef 2003 - *in silico*	33	0.56	linear
SLN 2f model	Group A19	149	0.21	linear
SLN 5f model	Group A19	149	0.50	linear
Pannier et al. (2003) – Fuzzy	94 compounds	94	0.82	non-linear
Pannier et al. (2003) – A NN	38 compounds	38	1.00	non-linear
Neely et al. (2009)	168 compounds	168	0.90	non-linear
GP 2f model	Group A19	149	0.32	non-linear
GP 5f model	Group A19	149	0.86	non-linear
MIXEXP 2f model	Group A19	149	0.28	non-linear
MIXEXP 5f model	Group A19	149	0.81	non-linear

Most developed QSPR models are based on multiple linear regression correlations requiring *a priori* assumption of the form of the mathematical correlation model. However, as already described earlier, linear regression analysis ignores the possibility of nonlinear descriptor relationships with the properties. The use of such linear approaches often leads to loss of critical information and results in models with poor predictive abilities. Therefore, the main objective was to introduce advanced machine learning techniques, including the GP method, a method not applied to skin permeability data before 2008. Following the review of the results, it was concluded that the GP model, based on the use of the human Group A19, yielded predictive algorithms that provided a significantly better estimate of skin absorption across a wider range of molecular properties than all the other QSPR models and naïve predictions when applied to the human skin dataset (A19, n = 149). It was particularly capable of providing excellent predictions where previous studies have shown QSPRs to fail at high log P and MW of penetrants. Furthermore, the GP model encompasses Flynn's conclusion that very hydrophilic and very hydrophobic compounds were represented by different mathematical relationships, suggesting, among other things, nonlinearity (Flynn 1990). When the GP model was compared to other nonlinear models available in the literature (Pannier et al. 2003; Neely et al. 2009), the resulting statistical fit was not equally good due to a possible increase in the variability in the structure of the compounds in each dataset. Even though GP analysis was performed based on a more refined dataset, the latter consisted of more diverse chemical structures, leading to a smaller statistical fit. Still, the GP model was easier to interpret and its development required a smaller number of data compared to other nonlinear models, such as those employing ANN (Kocijan et al. 2003).

The final component in the development of a newly constructed QSPR model is its validation. Validation of the model is generally accomplished by demonstrating its predictive ability. The model should be able to predict at a desired level of accuracy and the prediction error should be comparable to the error observed in the training and cross-validation sets. Therefore, the aim of the *in vitro* investigation conducted in this study was to compare the currently-developed models (i.e. the GP 5f model, the 5f linear model, the ionisation model and, for comparison reasons, the Potts and Guy 1992 model) and determine whether the experimentally-derived permeation data, obtained under carefully-controlled conditions (Appendix 3), correlated with those calculated from the application of the respective models. The experimental design involved the selection of drugs with different lipophilicities, whilst taking into account their suitability as potential model penetrants, to test the validity of the developed mathematical models. The selected drug candidates encompassed three different lipophilicity ranges. Three drugs were of low lipophilicity ($-1 < \log P > 1$), whereas a fourth one was of intermediate lipophilicity ($1 < \log P > 3$) and the final fifth drug was selected because of its high log P value ($\log P > 3$). Even though MW is also a very important factor when considering transdermal delivery, in order to avoid any possible influence from this parameter, relatively small molecules, with MW up to 350 Da, were selected.

It was concluded that all QSPR models developed in this study yielded better results with ionised molecules rather than with unionised molecules. This was due to the fact that most of the K_p values included in the datasets, upon which the QSPRs were developed, were measured from experiments in which the pH had not been controlled or reported during experimentation. As a result, in order to further investigate the pH effect, the

flux value of ibuprofen was investigated in three different pH environments. Even though in theory the unionised species is expected to penetrate the membrane to a greater extent than the ionised species, in this case it was found that as pH was increasing from 2.4 to 7.4, there was a concomitant increase in flux. This was probably due to the high solubility value obtained for the ionised molecules, as flux is the product of the permeability coefficient and the saturated concentration. It was shown that the permeability coefficients determined experimentally at pH 7.4 and 4.2 agreed with the predicted coefficients calculated from Equation 3.12. However, at pH 2.6, the predicted value did not match well with the experimental one. This might be due to the fact that, at such low pH, the solubility of the drug is small, which in turn leads to the generation of a relatively small flux and, thus, to a high K_p value, which might not be accommodated within the model, given the constraints of the training set.

In as much as the thesis has managed to survey the literature and propose an alternative model for skin permeability measurements, it only represents the starting point for a multitude of potential future research projects. These should address the problems and limitations already discussed and push forward towards the development of the most ideal computational model. Pathways along which research could progress in the future could include the following approaches.

In the current study, a series of datasets was assembled. As already discussed earlier, the most 'ideal' dataset constructed was Group A1 (11 compounds with ideal experimental criteria for the validation purposes), but, due to its small size, it cannot be very descriptive and, thus, cannot be used as a satisfactory training set for model development. For the actual experiment, the ideal experimental conditions were used as a baseline (as described by OECD 2004a, c). Ideally, more experiments approaching the *in vivo* situation should have existed in the literature so that in the selected groups (Groups A18 and A19, employed for the GP model development) data could be controlled to a greater extent. However, this was not the case and in order to obtain a satisfactory database in terms of both quality and size, parameters like skin thickness etc. were not taken into account; the only parameter controlled was the membrane employed. There is a need to generate new controlled data in the literature, derived under specific experimental conditions, in order to expand Group A1. The experimental conditions described in Chapter 2 are probably the best to adopt to ensure consistency. Specifically, the thickness of the membrane selected should fall within the range 0.2-0.5 mm, whereas the skin should be obtained from the human abdominal region. Additionally, only infinite dose experiments must be performed. Regarding the vehicle, buffer solutions must be employed in order to limit the ionisation effect. Flow-through diffusion cells must be used and the length of the study should not exceed 72 h. The temperature must also be maintained at 37 °C in the water bath with HPLC being the preferred analytical tool. Furthermore, for water-soluble compounds, the receiver fluid could be normal saline or isotonic buffer saline solutions, while for lipophilic compounds, the use of bovine serum albumin (4%) or PEG 20 (6%) is deemed to be acceptable. Even when it is difficult to conduct such specific experimental work, efforts should be made to improve and harmonise existing methodologies in order to minimise variability in any *in vitro* dermal absorption measurements. Hopefully, this lack of adequate 'ideal' data should encourage scientists to measure new data under carefully-controlled, agreed conditions and should also trigger research

workers to use these refined databases in order to develop further refined QSPR models. Even though such a task is hugely consumptive of time and intrinsically labour intensive, the validity of the model subsequently derived will be improved by a standardisation in the experimental protocol.

The GP model, derived from the use of 5 inputs, due to its nonlinearity, has yielded a predictive model that provides a significantly more accurate estimate of skin absorption than previous models across a wider range of molecular properties. It is capable of providing promising predictions across the range of log P values investigated, i.e. $-1 < \log P < 3.4$. However, as discussed previously, it does not take into consideration the ionisation effect as a factor that affects the permeability coefficient, as the log D values were left out of the model's development process. Even though this problem was partially resolved with the development of the ionisation equation described earlier (Equation 3.12), its linear nature is not a promising approach to be used in determining K_p. The incorporation of the log D values into the GP model should be considered as the next important step towards the development of a more robust nonlinear model. Nevertheless, caution should be taken when calculating the log D values, since for their determination log P for ionised species is required. Log P values for ionised compounds are hard to find in the literature. Alternatively, log D value can be determined by using the compound's pKa and pH. As a result, more studies should be conducted where the pH is monitored throughout the experiments.

It is acknowledged that even though the effect of lipophilicity in skin permeation was investigated, the effect of molecular size in skin absorption was not examined. Future work should seek to investigate the effect of molecular weight (MW) on skin penetration. Similarly to the experimental methodology applied in the current thesis, where the selected drug molecules encompassed three compounds with different lipophilicity, other molecules of different MW can be selected and the corresponding GP model can then be revalidated.

Finally, another point that should be taken into consideration in future model development is the formulation parameter. An additional parameter that could possibly be included in the model under development is the polarity of the formulation. If a penetrant dissolves better in the stratum corneum than in the formulation, then the active ingredient will prefer to distribute into the stratum corneum rather than remaining in the formulation. On the other hand, if the penetrant is too soluble in the formulation, it will not partition into the stratum corneum. This problem might be overcome by using the novel concept of a relative polarity index (RPI). It is essential to consider the stratum corneum as yet another solvent with its own polarity. The polarity is expressed by the octanol / water-partitioning coefficient. In order to use the concept of the RPI, three numbers (on log10 scale) are required, namely the polarity of the stratum corneum, the polarity of the penetrating molecule and the polarity of the formulation. The polarities of these three entities can be employed in the determination of the relevant polarity. The inclusion of this parameter in the K_p predictions could increase the predictive ability of a model, since much of the data available in the literature are applied in formulations.

The application of GP regression methods on datasets for membranes other than human skin was also examined. While the results of the latter investigation indicated that permeation across rodent (mouse and rat) and pig skin, in a statistical sense, was similar, artificial membranes proved to be poor replacements of human or animal skin.

While previous studies have been benchmarked against the Potts and Guy (1992) model due to its enormous contribution to this field and its widespread acceptance as the most frequently used quantitative model of percutaneous absorption, iterations of that model that include nonlinear terms might provide more substantial and realistic benchmarks. The new GP model makes reference to earlier work unnecessary by proposing a valid workable algorithm. A possible future alternation of the model allowing the incorporation of the ionisation effect should represent a new benchmark to be used by future model developers.

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Appendices

Appendix 1. Database A

Set 1: Flynn dataset - duplicates were excluded

No	Name	MW	Log P KOWWIN	Log K_p (cmh^{-1})
1	aldosterone	360.44	1.23	-5.52
2	amobarbital	226.27	2.00	-2.64
3	atropine	289.37	1.91	-5.07
4	barbital	184.19	0.60	-3.95
5	benzyl alcohol	108.19	1.08	-2.22
6	4-bromophenol	173.00	2.40	-1.44
7	2,3-butanediol	90.12	-0.36	-4.40
8	butyric acid	88.10	1.07	-3.00
9	n-butanol	74.12	0.84	-2.60
10	2-butanone	72.10	0.26	-2.35
11	butobarbital	212.24	1.59	-3.71
12	4-chlorocresol	142.58	2.70	-1.26
13	2-chlorophenol	128.55	2.16	-1.48
14	4-chlorophenol	128.55	2.16	-1.44
15	chloroxylenol	156.61	3.25	-1.28
16	chlorpheniramine	274.80	3.82	-2.66
17	codeine	299.30	1.28	-4.31
18	cortexolone	346.44	3.15	-4.13
19	cortexone	330.45	3.12	-3.35
20	corticosterone	346.46	1.99	-4.22
21	cortisone	360.44	1.20	-5.00
22	2-cresol	108.14	2.06	-1.80
23	3-cresol	108.14	2.06	-1.82
24	4-cresol	108.14	2.06	-1.75
25	n-decanol	158.28	3.79	-1.10
26	2,4-dichlorophenol	163.00	2.80	-1.22
27	diethylcarbamazine	199.29	0.37	-3.89
28	digitoxin	764.94	2.04	-4.89
29	ephedrine	165.23	0.68	-2.22
30	estradiol	272.39	3.94	-3.52
31	estriol	288.38	2.81	-4.40
32	estrone	270.37	3.43	-2.44
33	ethanol	46.06	-0.14	-3.10
34	2-ethoxyethanol	90.12	-0.42	-3.60
35	ethyl benzene	106.16	3.03	-0.08
36	ethyl ether	74.12	1.05	-1.80
37	4-ethyl phenol	122.16	2.55	-1.46
38	etorphine	409.52	3.02	-2.44
39	fentanyl	336.47	3.89	-2.25
40	fluocinonide	494.55	2.77	-2.77
41	heptanoic acid	130.18	2.54	-1.70
42	n-heptanol	116.20	2.31	-1.50
43	hexanoic acid	116.16	2.05	-1.85
44	n-hexanol	102.17	1.82	-1.89
45	hydrocortisone	362.46	1.62	-5.52
46	(hydrocortisone-21-yl)-hemipimelate	504.60	3.26	-2.75
47	(hydrocortisone-21-yl)-NN dimethyl succinate	489.60	2.03	-4.17
48	(hydrocortisone-21-yl)-hexanoate	460.60	4.48	-1.75
49	(hydrocortisone-21-yl)-hydroxy hexanoate	476.60	2.79	-3.04
50	(hydrocortisone-21-yl)-octanoate	488.70	5.49	-1.21

No	Name	MW	Log P KOWWIN	Log K_p (cmh^{-1})
51	(hydrocortisone-21-yl)-pimelamate	503.60	2.31	-3.05
52	(hydrocortisone-21-yl)-propionate	418.50	2.80	-2.47
53	(hydrocortisone-21-yl)-succinate	461.60	1.43	-4.59
54	(hydrocortisone-21-yl)-hemisuccinate	489.60	2.11	-1.01
55	hydromorphone	285.30	1.60	-4.82
56	hydroxypregnenolone	330.45	3.71	-3.22
57	17-a-hydroxyprogesterone	330.46	3.08	-3.22
58	isoquinoline	129.16	2.14	-1.78
59	meperidine	247.33	3.03	-2.43
60	methanol	32.04	-0.63	-3.30
61	methyl-(hydrocortisone-21-yl)-succinate	476.60	2.58	-3.68
62	methyl- (hydrocortisone-21-yl)-pimelamate	518.60	3.70	-2.27
63	methyl-4-hydroxy benzoate	152.14	1.96	-2.04
64	morphine	287.35	0.72	-5.03
65	2-naphtol	144.16	2.69	-1.55
66	naproxene	230.26	3.10	-3.40
67	nicotine	162.23	1.00	-1.71
68	nitroglycerine	227.09	1.51	-1.96
69	3-nitrophenol	139.11	1.91	-2.25
70	4-nitrophenol	139.11	1.91	-2.25
71	n-nitrosodiethanolamine	134.13	-1.28	-5.22
72	n-nonanol	144.26	3.30	-1.22
73	octanoic acid	144.21	3.03	-1.60
74	n-octanol	130.23	3.15	-1.28
75	oubain	584.64	-2.83	-6.11
76	pentanoic acid	102.13	1.56	-2.70
77	n-pentanol	88.14	1.33	-2.22
78	phenobarbital	232.23	1.33	-3.34
79	phenol	94.11	1.51	-2.09
80	pregnenolone	316.47	3.89	-2.82
81	progesterone	314.46	3.67	-2.82
82	n-propanol	60.09	0.35	-2.85
83	resorcinol	110.11	1.03	-3.62
84	salicylic acid	138.12	2.24	-2.20
85	scopolamine	303.35	0.39	-4.30
86	styrene	104.15	2.89	-0.19
87	sucrose	342.29	-4.27	-5.28
88	sufentanil	367.50	3.62	-1.92
89	testosterone	288.42	3.27	-3.40
90	thymol	150.22	3.52	-1.28
91	toluene	92.14	2.54	0.00
92	2,4,6 trichlorophenol	197.45	3.45	-1.23
93	water	18.01	-1.38	-3.30
94	3,4 xylenol	122.17	2.61	-1.44

Set 2: Wilshut dataset

No	Name	MW	Log P KOWWIN	Log K_p (cmh^{-1})
1	water	18.00	-1.38	-2.81
2	urea	60.60	-1.56	-3.83
3	benzene	78.10	1.99	-0.95
4	ephedrine	165.20	0.68	-2.22
5	scopolamine	303.40	0.39	-4.30

No	Name	MW	Log P KOWWIN	Log K_p (cmh^{-1})
6	diethylcarbamazine	199.30	0.37	-3.95
7	oubain	584.64	-2.83	-6.11
8	digitoxin	764.90	2.04	-4.89
9	chlorpheniramine	274.80	3.82	-2.66
10	nitroglycerine	227.10	1.51	-1.96
11	fentanyl	336.50	3.89	-2.00
12	estradiol	272.40	3.94	-2.28
13	atropine	289.40	1.91	-5.07
14	water	18.00	-1.38	-3.70
15	water	18.00	-1.38	-3.30
16	heptanol	116.20	2.31	-1.49
17	propanol	60.10	0.35	-2.92
18	ethanol	46.10	-0.14	-3.10
19	methanol	32.00	-0.63	-3.30
20	nonanol	144.30	3.30	-1.22
21	decanol	158.30	3.79	-1.10
22	n-butanol	74.10	0.84	-2.60
23	octanol	130.20	3.15	-1.28
24	hexanol	102.20	1.82	-1.89
25	pentanol	88.20	1.33	-2.22
26	methylhydroxybenzoate	152.10	1.96	-2.04
27	b-naphtol	144.20	2.69	-1.55
28	2,4-dichlorophenol	163.00	2.80	-1.22
29	p-bromophenol	173.00	2.40	-1.44
30	m-nitrophenol	139.10	1.91	-2.25
31	p-cresol	108.10	2.06	-1.76
32	p-nitrophenol	139.10	1.91	-2.25
33	o-cresol	108.10	2.06	-1.80
34	3,4-xylenol	122.10	2.61	-1.44
35	2,4,6-trichlorophenol	197.50	3.45	-1.23
36	chloroxylenol	156.60	3.25	-1.23
37	phenol	94.10	1.51	-2.09
38	p-ethylphenol	122.20	2.55	-1.46
39	resorcinol	110.10	1.03	-3.62
40	p-chlorophenol	128.60	2.16	-1.44
41	thymol	150.20	3.52	-1.28
42	o-chlorophenol	128.60	2.16	-1.48
43	chlorocresol	142.60	2.70	-1.26
44	m-cresol	108.10	2.06	-1.82
45	naproxen	230.30	3.10	-3.40
46	piroxicam	331.40	2.58	-3.81
47	indomethacin	357.80	4.23	-3.67
48	naproxen	230.30	3.10	-3.15
49	salicylic acid	138.10	2.24	-3.48
50	phenol	94.10	1.51	-1.71
51	diclofenac	318.00	4.02	-3.45
52	barbital	184.20	0.60	-3.95
53	nicotine	162.30	1.00	-1.72
54	isoquinoline	129.20	2.14	-1.78
55	amylobarbital	226.30	2.00	-2.64
56	phenobarbital	232.20	1.33	-3.35
57	hydrocortisone	362.50	1.62	-3.92
58	butobarbital	212.40	1.59	-3.72

No	Name	MW	Log P KOWWIN	Log K_p (cmh^{-1})
59	salicyclic acid	138.10	2.24	-2.20
60	2-ethoxyethanol	90.10	-0.42	-3.60
61	1,1,1-trichloroethane	133.40	2.68	-2.35
62	n-butanol	74.10	0.84	-2.52
63	heptanol	116.20	2.31	-1.42
64	ethyl ether	74.10	1.05	-2.80
65	propanol	60.10	0.35	-2.77
66	water	18.00	-1.38	-2.85
67	hexanol	102.20	1.82	-1.56
68	testosterone	288.40	3.27	-3.40
69	estriol	288.40	2.81	-4.40
70	hydroxypregnenolone	330.50	3.71	-3.22
71	cortisone	360.50	1.20	-5.00
72	pregnenolone	316.50	3.89	-2.82
73	cortexone	330.50	3.12	-3.35
74	progesterone	314.50	3.67	-2.82
75	cortexolone	346.50	3.15	-4.12
76	hydrocortisone	362.50	1.62	-5.52
77	corticosterone	346.50	1.99	-4.22
78	hydroxyprogesterone	330.50	3.08	-3.22
79	estrone	270.40	3.43	-2.44
80	aldosterone	360.40	1.23	-5.52
81	estradiol	272.40	3.94	-3.52
82	hydrocortisone methylsuccinate	476.60	5.58	-3.68
83	hydrocortisone hexanoate	460.60	4.48	-1.74
84	hydrocortisone methylpimelate	518.60	3.70	-2.27
85	hydrocortisone N,N,-dimethylsuccinate	489.60	2.03	-4.17
86	hydrocortisone hemisuccinate	462.50	2.11	-3.20
87	fluocinonide	494.60	2.77	-2.77
88	hydrocortisone octanoate	488.70	5.49	-1.21
89	hydrocortisone propinate	418.50	2.80	-2.47
90	hydrocortisone succinamate	461.60	1.43	-4.59
91	hydrocortisone hydroxyhexanoate	476.60	2.79	-3.04
92	hydrocortisone hemipimelate	503.60	3.26	-2.74
93	hydrocortisone pimelamate	503.60	2.31	-3.05
94	sucrose	342.30	-4.27	-5.28
95	propanol	60.10	0.34	-2.85
96	ethanol	46.10	-0.14	-3.00
97	water	18.00	-1.38	-3.00
98	hexanol	102.20	1.82	-1.89
99	methanol	32.00	-0.63	-3.00
100	octanol	130.20	3.15	-1.28
101	heptanol	116.20	2.31	-1.49
102	pentanol	88.20	1.33	-2.22
103	n-butanol	74.10	0.84	-2.60
104	o-phenylenediamine	108.10	0.15	-3.35
105	2-nitro p-phenylenediamine	153.10	0.53	-3.30
106	p-phenylenediamine	108.10	-0.30	-3.62
107	4-amino-2-nitrophenol	154.10	0.96	-2.55
108	4-chloro-m-phenylenediamine	142.60	0.85	-2.68
109	2-amino-4-nitrophenol	154.10	1.13	-3.18
110	benzyl alcohol	108.10	1.08	-1.77
111	benzaldehyde	106.10	1.71	-0.85

No	Name	MW	Log P KOWWIN	Log K_p (cmh^{-1})
112	aniline	93.10	0.90	-1.66
113	anisole	108.10	2.07	-1.60
114	2-phenylethanol	122.20	1.57	-1.42
115	etorphine	411.50	3.02	-2.44
116	sufentanil	386.60	3.62	-2.26
117	fentanyl	336.50	3.89	-2.52
118	meperidine	247.40	3.03	-2.43
119	sufentanil	386.60	3.62	-1.92
120	morphine	285.30	0.72	-5.03
121	codeine	299.40	1.28	-4.31
122	fentanyl	336.50	3.89	-2.25
123	hydromorphone	285.30	1.60	-4.82

Set 3. Cronin dataset

No	Name	MW	Log P KOWWIN	Log K_p (cmh^{-1})
1	folmaldehyde	30.03	0.35	-2.65
2	methanol	32.04	-0.63	-3.46
3	acetonitrile	41.05	-0.15	-3.21
4	acrylonitrile	53.06	0.21	-2.87
5	monomethylhydrazine	46.07	-1.00	-3.75
6	ethanol	46.07	-0.14	-3.10
7	acetaldehyde	44.05	-0.17	-3.15
8	propylene oxide	58.08	0.37	-3.05
9	acrolein	56.06	0.19	-3.07
10	allyl alcohol	58.08	0.21	-2.95
11	ethylene glycol	62.07	-1.20	-4.07
12	acetic acid	60.05	0.09	-3.21
13	ethylamine	45.08	-0.15	-3.09
14	ethanolamine	61.08	-1.61	-4.02
15	acrylic acid	72.06	0.44	-3.05
16	epichlorohydrin	92.52	0.63	-3.43
17	isopropyl alcohol	60.10	0.28	-3.05
18	acetone	58.08	-0.24	-3.29
19	n-propanol	60.10	0.35	-2.91
20	ethylene dichloride	98.96	1.83	-2.00
21	methyl cellosolve	76.09	1.83	-3.73
22	ethyl formate	74.08	0.32	-3.01
23	pyridine	79.10	0.80	-2.74
24	dioxane	88.11	-0.32	-3.45
25	isopropylamine	59.11	0.27	-2.90
26	propionic acid	74.08	0.58	-2.94
27	vinyl acetate	86.09	0.73	-2.73
28	morpholine	87.12	-0.54	-3.86
29	methyl acrylic acid	86.09	0.99	-2.58
30	methyl acrylate	86.09	0.73	-2.68
31	phenol	94.11	1.51	-2.00
32	diethyl ether	74.12	0.89	-1.80
33	n-butanol	74.12	0.84	-1.55
34	isobutanol	74.12	0.77	-2.65
35	2-butanone	72.11	0.26	-2.95
36	butyric acid	88.11	1.07	-3.00
37	resorcinol	110.11	1.03	-2.82

No	Name	MW	Log P KOWWIN	Log K_p (cmh^{-1})
38	diethylamine	73.14	0.58	-2.75
39	catechol	110.11	0.88	-2.77
40	2,3-butanediol	90.12	-0.36	-4.39
41	aniline	93.13	0.90	-2.65
42	toluene	92.14	2.54	-1.30
43	dimethylacetamide	87.12	-0.49	-2.80
44	ethyl acrylate	100.12	1.32	-2.39
45	1,2-dichloropropene	110.97	1.76	-2.00
46	4-chlorophenol	128.56	2.16	-1.44
47	2-chlorophenol	128.56	2.16	-1.48
48	styrene	104.15	2.89	-0.19
49	benzyl alcohol	108.14	1.08	-2.22
50	4-cresol	108.14	2.06	-2.00
51	2-pentanone	86.13	0.91	-2.60
52	3-cresol	108.14	2.06	-2.00
53	cyclohexanone	98.14	0.81	-2.74
54	diethanolamine	105.14	-1.71	-4.38
55	isoamyl alcohol	88.15	1.16	-2.00
56	n-pentanol	88.15	1.33	-2.22
57	2-cresol	108.14	2.06	-2.00
58	4-bromophenol	173.01	2.40	-1.44
59	pentanoic acid	102.13	1.56	-2.70
60	2-toluidine	107.16	1.62	-1.44
61	ethylbenzene	106.17	3.03	-1.15
62	3-xylene	106.17	3.09	-1.10
63	n-nitrosodiethanolamine	134.13	-1.28	-5.22
64	2,4-dichlorophenol	163.00	2.80	-1.22
65	salicylic acid	138.12	2.24	-2.20
66	isoquinoline	129.16	2.14	-1.78
67	4-methyl-2-pentanol	102.18	1.68	-2.33
68	n-hexanol	102.18	1.82	-1.89
69	4-ethylphenol	122.17	2.55	-1.46
70	2-hexanone	100.16	1.24	-2.35
71	2-butoxyethanol	118.18	0.57	-2.85
72	triethylamine	101.19	1.45	-2.31
73	N,N-dimethylaniline	121.18	2.31	-1.70
74	phenylglycidyl ether	150.18	1.61	-2.84
75	hexanoic acid	116.16	2.05	-1.85
76	2,4,6-trichlorophenol	197.45	3.45	-1.23
77	butyl acrylate	128.17	2.36	-2.00
78	hexachloroethane	236.74	4.03	-1.40
79	cumene	120.19	3.45	-0.85
80	4-chloro-3,5-xylenol	156.61	3.25	-1.28
81	2-heptanone	114.19	2.31	-2.00
82	n-heptanol	116.20	2.31	-1.50
83	heptanoic acid	130.19	2.54	-1.70
84	n-octanol	130.23	3.15	-1.28
85	nicotine	162.23	1.00	-1.71
86	thymol	150.22	3.52	-1.28
87	octanoic acid	144.21	3.03	-1.60
88	hexachlorobutadiene	260.76	4.72	-0.92
89	n-decanol	158.28	3.79	-1.10
90	phenobarbital	232.24	1.33	-3.34

No	Name	MW	Log P KOWWIN	Log K_p (cmh^{-1})
91	butobarbital	212.25	1.59	-3.71
92	naproxen	230.26	3.10	-3.40
93	amobarbital	226.27	2.00	-2.64
94	hydromorphone	285.34	1.60	-4.82
95	morphine	285.34	0.72	-5.03
96	meperidine	247.34	3.03	-2.43
97	estrone	270.37	3.03	-2.44
98	scopolamine	303.36	0.39	-4.30
99	testosterone	288.43	3.27	-3.40
100	aldosterone	360.45	1.23	-5.52
101	progesterone	314.47	3.67	-2.82
102	17-hydroxyprogesterone	330.47	3.08	-3.22
103	cortexolone	346.46	3.15	-4.13
104	fentanyl	336.48	3.89	-2.25
105	corticosterone	346.46	1.99	-4.22
106	cortisone	360.45	1.20	-5.00
107	ethylhexyl phthalate	390.56	8.39	-1.52

Appendix 2. Database B

Human skin dataset – Experimental permeability coefficients and drug properties

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	K_p (cmh^{-1})	Log K_p (cmh^{-1})
1	salicyclic acid	138.10	2.26 –a	13.13	0.006264	-2.20 – a
2	isoquinoline	129.20	2.03 –a	11.53	0.016812	-1.77 – a
3	amylobarbital	226.30	1.96 –a	12.27	0.002268	-2.64 – a
4	butabarbital	212.20	1.89 –a	13.13	0.000194	-3.71 – a
5	phenobarbital	232.20	1.47 –a	14.42	1.645200	0.22 – a
6	barbital	184.20	0.65 –a	14.20	0.000112	-3.95 – a
7	progesterone	314.50	3.70 –a	9.85	0.001512	-2.82 – a
8	pregnenolone	316.50	3.13 –a	10.91	0.001512	-2.82 – a
9	hydroxyprogesterone	332.50	2.47 –a	10.91	0.000598	-3.22 – a
10	hydroxypregnenolone	330.50	3.00 –a	10.91	0.000598	-3.22 – a
11	deoxycorticosterone	330.50	2.88 –a	18.37	0.000450	-3.35 – a
12	testosterone	288.40	3.31 –a	10.87	0.000396	-3.40 – a
13	cortexolone	346.50	2.52 –a	18.37	0.000076	-4.12 – a
14	corticosterone	346.50	1.94 –a	18.37	0.000061	-4.21 – a
15	cortisone	360.50	1.42 –a	18.37	0.000011	-4.97 – a
16	estrone	270.40	2.76 –a	14.51	0.003600	-2.44 – a
17	estradiol	272.40	2.69 –a	12.01	0.000288	-3.54 – a
18	estriol	288.40	2.47 –a	20.04	0.000040	-4.40 – a
19	methanol	32.00	4.77 –a	13.77	0.001008	-3.00 – a
20	ethanol	46.00	-0.31 –a	12.58	0.001008	-3.00 – a
21	propan-1-ol	60.00	0.25 –a	11.84	0.001404	-2.85 – a
22	butan-1-ol	74.00	0.88 –a	11.33	0.002484	-2.60 – a
23	pentan-1-ol	88.00	1.56 –a	10.96	0.005976	-2.22 – a
24	hexan-1-ol	102.20	2.03 –a	10.68	0.013068	-1.88 – a
25	heptan-1-ol	116.20	2.72 –a	10.46	0.032040	-1.49 – a
26	octan-1-ol	130.20	2.97 –a	10.28	0.052200	-1.28 – a
27	oxprenolol	265.40	2.62 –b	11.03	0.001549	-2.81 – b
28	metoprolol	267.40	2.28 –b	10.93	0.000832	-3.08 – b
29	atenolol	266.30	1.95 –b	13.24	0.061660	-1.21 – b
30	griseofulvin	352.80	2.07 – d	10.44	0.001288	-2.89 – d
31	griseofulvin	352.80	2.07 – d	10.44	0.001950	-2.71 – d
32	propranolol	295.84	0.56 – b	11.96	0.070795	-1.15 – b
33	indomethacin	357.80	3.08 – e	12.35	0.000009	-5.39 – e
34	ibuprofen	206.30	3.51 – e	10.00	0.036308	-1.44 – e
35	morphine	285.30	0.62 – c	13.10	0.000009	-5.03 – c
36	hydromorphine	285.30	1.25 – c	11.70	0.000015	-4.82 – c
37	codeine	299.30	0.89 – c	10.90	0.000049	-4.31 – c
38	fentanyl	336.50	4.37 – c	9.80	0.010000	-2.00 – c
39	sufentanyl	387.50	4.59 – c	9.70	0.012023	-1.92 – c
40	meperidine	247.00	2.72 – c	9.60	0.003715	-2.43 – c
41	dexamethasone	392.47	1.83 – k	11.98	0.000065	-4.19 – k
42	corticosterone	346.45	3.32 – i	18.37	0.000891	-3.05 – i
43	atenolol	266.00	1.77 – j	13.24	0.000145	-3.84 – j
44	hydrocortisone 21 - (N/N -dime) succ	489.61	2.03 – a	12.22	0.000068	-4.17 – a
45	hydrocortisone 21 propionate	418.50	3.00 – a	12.33	0.003388	-2.47 – a
46	hydrocortisone 21 - pimelamate	503.63	2.31 – a	14.23	0.000891	-3.05 – a
47	hydrocortisone 21 - octanoate	488.66	5.49 – a	10.55	0.061660	-1.21 – a
48	hydrocortisone 21 - methylsuccinate	476.57	2.58 – a	12.44	0.000209	-3.68 – a
49	hydrocortisone 21 - methylpimelate	518.65	3.70 – a	11.39	0.005370	-2.27 – a
50	hydrocortisone 21 - hexanoate	460.61	4.48 – a	11.01	0.017783	-1.75 – a

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	K_p (cmh^{-1})	Log K_p (cmh^{-1})
51	hydrocortisone 21 - hemisuccinate	462.54	2.11 – a	14.48	0.000631	-3.20 – a
52	hydrocortisone 21 - hemipimelate	504.62	2.31 – a	12.68	0.002778	-2.75 – a
53	hydrocortisone 21 (6-OH) hexanoate	476.61	2.79 – a	13.82	0.000912	-3.04 – a
54	hydrocortisone 21 - succinamate	461.60	1.43 – a	16.90	0.000026	-4.59 – a
55	bufexamac	223.30	2.43 – f	13.33	0.004169	-2.38 – f
56	diclofenac sodium	318.10	4.40 – f	12.76	0.000355	-3.45 – f
57	felbinac	212.20	3.26 – f	11.86	0.019055	-1.72 – f
58	flurbiprofen	244.30	4.12 – f	11.62	0.048978	-1.31 – f
59	naproxen	230.30	3.00 – f	11.47	0.002884	-2.54 – f
60	aspirin	180.16	1.02 – g	12.21	0.007244	-2.14 – g
61	benzoic acid	122.10	1.88 – h	11.52	0.025119	-1.60 – h
62	sucrose	342.30	-2.25 – i	16.07	0.000005	-5.28 – i
63	b-estradiol	272.37	2.69 – i	12.01	0.005248	-2.28 – i
64	phenol	94.11	1.46 – i	13.46	0.008128	-2.09 - i
65	raffinose	504.00	-4.30 – j	18.73	0.000083	-4.08 – j
66	mannitol	182.00	-3.10 – j	18.53	0.001122	-2.95 – j
67	salicyclic acid	138.00	-2.14 – j	13.13	0.000646	-3.19 – j
68	pindolol	248.00	-0.33 – j	12.10	0.000282	-3.55 – j
69	alprenolol	249.00	0.65 – j	10.86	0.002291	-2.64 – j
70	aldosterone	360.04	1.08 – j	18.37	0.000159	-3.80 – j

References
a - from Ghafourian & Fooladi (2001)
b - from Modamio et al. (2000)
c - from Roy & Flynn (1989)
d - from Ritschel et al. (1989)
e - from Hadgraft et al. (2000a)
f - from *The Pharmaceutical Codex*
g - from Fang et al. (2003)
h - from Degim et al. (1998)
i - from the Flynn dataset (1990)
j - from Suhonen et al. (2003)
k - from Johnson et al. (1997)

Mouse skin dataset – Experimental permeability coefficients and drug properties

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	K_p (cmh^{-1})	Log K_p (cmh^{-1})
1	theophylline	180.00	-0.25 – b	14.05	0.6600	-0.18 – a
2	5 fluorouracil	130.01	2.70 – b	14.99	4.3100	0.63 – a
3	bis (1-piperindyl) methyl 5 FU	324.00	2.70 – b	11.04	0.0110	-1.96- a
4	1,3 bis (4-morpholinyl) methyl 5FU	328.00	2.70 – b	11.46	0.0430	-1.37 – a
5	7-(dibutylamino) methyl theophylline	321.00	-0.25 – b	10.98	0.0035	-2.46 – a
6	7-(piperindyl) methyl theophylline	277.00	-0.25 – b	12.04	0.0140	-1.85 – a
7	progesterone	314.50	3.70 – d	10.91	0.0756	-1.12 – c
8	estradiol	272.40	2.69 – d	12.01	0.0079	-2.10 – c
9	hydrocortisone	362.50	1.53 – e	12.38	0.0004	-3.44 – c
10	ethanol	46.00	-0.31 – f	12.58	0.0027	-2.57 – f
11	propanol	60.00	0.21 – f	11.84	0.0043	-2.37 – f
12	butanol	74.00	0.83 – f	11.33	0.0087	-2.06 – f
13	pentanol	88.00	1.37 – f	10.96	0.0163	-1.79 – f
14	hexanol	102.20	2.02 – f	10.68	0.0317	-1.50 – f
15	heptanol	116.20	2.40 – f	10.46	0.0704	-1.15 – f
16	octanol	130.20	2.97 – f	10.28	0.1289	-0.89 – f
17	methanol	32.00	-0.70 – f	13.77	0.0037	-2.43 – f

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	K_p (cmh^{-1})	Log K_p (cmh^{-1})
18	fentanyl	336.50	4.37 – h	9.80	0.0081	-2.09 – g
19	estradiol	272.40	2.69 – d	12.01	0.0159	-1.80 – g
20	mannitol	182.00	-3.10 – i	18.53	0.0009	-3.06 – g
21	corticosterone	346.50	1.94 – j	18.37	0.0008	-3.10 – j
22	corticosterone (PVP/PBS)	346.50	1.94 – j	18.37	0.0009	-3.06 – j
23	atenolol	266.34	-1.83 – k	13.24	0.2800	-0.55 – k
24	propranolol	295.30	0.56 – k	11.96	0.00005	-4.35 – k
25	propranolol HCL	295.84	0.56 - k	11.96	0.0750	-1.12 – k
26	oxprenolol	301.80	2.37 - k	11.03	0.0052	-2.28 – k
27	prednisolone heptanoate	472.62	4.08 – l	12.02	0.0001	-4.11 – l
28	prednisolone octanoate	486.65	4.39 – l	11.89	0.0001	-3.96 – l
29	prednisolone nonanoate	500.68	4.66 – l	11.78	0.0001	-4.04 – l
30	prednisolone decanoate	514.70	5.15 – l	11.67	0.0001	-3.95 – l
31	prednisolone undecanoate	528.73	5.54 – l	11.57	0.0002	-3.83 – l
32	prednisolone tridecanoate	556.78	6.02 – l	11.39	0.0001	-3.97 – l
33	prednisolone pentadecanoate	584.84	6.79 – l	11.23	0.0001	-4.01 – l
34	metoprolol	267.00	1.88 – k	10.93	0.0028	-2.56 – k
35	nifedipine	346.30	3.14 – m	11.23	0.0017	-2.77 – m
36	diclofenac sodium	318.10	1.13 – n	12.76	0.0003	-3.54 – n
37	hydrocortisone	362.50	1.53 – e	12.38	0.0001	-3.92 – e
38	hydrocortisone (DPY)	362.50	1.53 – e	12.38	0.0026	-2.59 – e
39	hydrocortisone (DPI)	362.50	1.53 – e	12.38	0.0025	-2.61 – e
40	hydrocortisone (DMEA)	362.50	1.53 – e	12.38	0.0016	-2.81 – e
41	hydrocortisone (DMEI)	362.50	1.53 – e	12.38	0.0006	-3.22 – e
42	hydrocortisone (DDE)	362.50	1.53 – e	12.38	0.0008	-3.08 – e
43	hydrocortisone (ND)	362.50	1.53 – e	12.38	0.0007	-3.13 – e

References
a - from Waranis & Sloan (1987)
b - from *The Pharmaceutical Codex*
c - from Knutson et al. (1993)
d - from Ghafourian & Fooladi (2001)
e - from Fuhrman et al. (1997)
f - from Shah et al. (1991)
g - from Liaw & Lin (2000)
h - from Roy & Flynn (1989)
i - from Suhonen et al. (2003)
j - from Shaker (2003)
k - from Ghosh et al. (1992)
l - from Hashiguchi et al. (1997)
m - from Diez et al. (1991)
n - from Arellano et al. (1996)
o - from Jain et al. (1995)

Rat skin dataset – Experimental permeability coefficients and drug properties

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	K_p (cmh^{-1})	Log K_p (cmh^{-1})
1	raffinose	504.00	-4.30 – a	18.73	0.00004	-4.42 – a
2	mannitol	182.00	-3.10 – a	18.53	0.00302	-2.52 – a
3	salicyclic acid	138.00	-2.14 – a	13.13	0.00012	-3.91 – a
4	atenolol	266.00	-1.77 – a	13.24	0.00045	-3.35 – a
5	pindolol	248.00	-0.33 – a	12.10	0.00037	-3.43 – a
6	metoprolol	267.00	0.03 – a	10.93	0.00017	-3.77 – a
7	alprenolol	249.00	0.65 – a	10.88	0.00447	-2.35 – a

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	K_p (cmh^{-1})	Log K_p (cmh^{-1})
8	aldosterone	360.04	1.08 – a	18.37	0.00013	-3.89 – a
9	corticosterone	347.00	1.94 – a	18.37	0.00135	-2.87 – a
10	testosterone	288.00	3.32 – a	10.87	0.04898	-1.31 – a
11	b-estradiol	272.00	3.86 – a	12.01	0.05888	-1.23 – a
12	b-estradiol	272.00	3.86 – b	12.01	0.09772	-1.01 – b
13	ibuprofen	206.30	3.51 – b	10.25	0.36308	-0.44 – b
14	flurbiprofen	244.30	4.12 – b	11.62	0.40738	-0.39 – b
15	indomethacin	357.80	3.08 – b	12.35	0.15136	-0.82 – b
16	morphine	285.30	0.62 – b	13.10	0.00046	-3.34 – b
17	hydrocortisone (azone)	326.47	1.53 – c	12.38	0.00132	-2.88 – c
18	hydrocortisone	326.47	1.53 – c	12.38	0.00012	-3.92 – c
19	hydrocortisone (DPY)	326.47	1.53 – c	12.38	0.00204	-2.69 – c
20	hydrocortisone (DPI)	326.47	1.53 – c	12.38	0.00178	-2.75 – c
21	hydrocortisone (DMEA)	326.47	1.53 – c	12.38	0.00069	-3.16 – c
22	hydrocortisone (DMEI)	326.47	1.53 – c	12.38	0.00076	-3.12 – c
23	hydrocortisone (DDE)	326.47	1.53 – c	12.38	0.00141	-2.85 – c
24	hydrocortisone (ND)	326.47	1.53 – c	12.38	0.00076	-3.27 – c
25	aspirin	180.16	1.23 – d	11.81	0.00141	-0.46 – d
26	naproxen	230.26	3.18 – d	11.47	0.00054	-1.37 – d
27	flurbiprofen	244.26	3.86 – d	11.62	0.34674	-2.48 – d
28	nifedipine	346.30	3.14 – e	12.16	0.04266	-2.77 – e
29	5 - fluorouracil	130.01	-0.86 – b	14.99	0.00331	-3.76 – b
30	barbital	184.20	0.65 – b	14.20	0.00170	-2.38 – b
31	sucrose	342.00	-3.70 – h	16.07	0.00174	-3.02 – g
32	5 - FU (SLS 1%)	130.01	-0.86 – e	14.99	0.00331	-2.37 – e
33	5 - FU (SLS 5%)	130.01	-0.86 – e	14.99	0.00170	-2.34 – e
34	indomethacin (SLS 1%)	357.86	3.08 – e	12.35	0.00017	-1.09 – e
35	propranolol	259.00	3.56 – f	11.96	0.00407	-2.39 – f
36	bufexamac	223.30	2.43 – d	13.33	0.26915	-0.57 – d

References
a - from Suhonen et al. (2003)
b - from Hatanaka et al. (1992)
c - from Fuhrman et al. (1997)
d - from Fang et al. (2003)
e - from Borras-Blasco et al. (1997)
f - from Diez et al. (1991)
g - from Peck et al. (1998)
h - from Johnson et al. (1997)

Silicone membrane dataset – Experimental permeability coefficients and drug properties

No	Drug	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	K_p (cmh^{-1})	Log K_p (cmh^{-1})
1	estradiol	272.40	2.69 - a	12.01	0.262080	-0.58 – a
2	ibuprofen	206.30	3.51 – a	10.25	12.63600	1.10 – a
3	flurbiprofen	244.30	3.86 – a	11.62	2.642400	0.42 – a
4	indomethacin	357.80	3.09 – a	12.35	0.063000	-1.20 – a
5	barbital	184.20	0.87 – a	14.20	0.002690	-2.57 – a
6	5 - fluorouracil	130.01	-0.86 – a	14.99	0.000004	-5.37 – a
7	benzoic acid	122.10	1.88 – b	12.70	0.057000	-1.24 – b
8	salicyclic acid	138.10	2.26 – b	13.13	0.160000	-0.80 – b
9	phenol	94.11	1.49 – c	13.46	0.129000	-0.89 – c
10	diazepam	284.75	2.92 – c	11.52	0.450000	-0.35 – c
11	2-nitrophenol	139.11	1.79 – c	13.19	1.233000	0.09 – c

No	Drug	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	K_p (cmh^{-1})	Log K_p (cmh^{-1})
12	3-nitrophenol	139.11	2.00 – c	13.19	0.045000	-1.35 – c
13	4-nitrophenol	139.11	1.91 – c	13.19	0.030000	-1.52 – c
14	nitrobenzene	123.11	1.85 – c	10.45	2.009000	0.30 – c
15	2-bromophenol	173.02	2.35 – c	15.17	0.701000	-0.15 – c
16	4-bromophenol	173.02	2.59 – c	15.17	0.360000	-0.44 – c
17	hydrocortisone	362.50	1.53 – b	12.38	0.000074	-4.13 – d
18	hydrocortisone -21- hexanoate	460.61	4.48 – b	11.01	0.001480	-2.83 – d

References

a - from Hatanaka et al. (1992)
b - from the Flynn dataset (1990)
c - from Geinoz et al. (2002)
d - from Hagen et al. (1987)

Appendix 3. Database C

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
1	5-fluorouracil	human	130.01	13.46	-0.81	3	2	0.0000166	-4.78	0.002% aq. sodium azide solution	dermatomed 0.42 mm	abdomen	flow-through	0.002% aq.sodium azide solution	31	24	radiolabelled (3H)	*J.Investig.Pharmacol.*, 94: 235-240
2	water	human	18.02	26.68	-1.38	1	1	0.0013	-2.89	none	dermatomed 0.42 mm	abdomen	flow-through	0.002% sodium azide solution	31 (skin)	6	radiolabelled (3H)	*J.Invest.Dermatol.*, 94: 235-240
3	nicotine	human	162.3	11.25	1	2	0	0.0103	-1.99	0.05M phosphate buffer	dermatomed 0.41 mm	abdomen/breast	static	0.05M phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm. Sci.*, 11: 59-68
4	N-N-diethyl m-toluamide	human	191.28	10.70	2.26	1	0	0.000581	-3.24	45% aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67: 211-221
5	N-N-diethyl m-toluamide	human	191.28	10.70	2.26	1	0	0.000598	-3.22	60 % aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67: 211-221
6	N-N-diethyl m-toluamide	human	191.28	10.70	2.26	1	0	0.000099	-4.00	90 % aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67: 211-221
7	N-N-diethyl m-toluamide	human	191.28	10.70	2.26	1	0	0.0000632	-4.20	none	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67: 211-221
8	N-N-diethyl m-toluamide	human	191.28	10.70	2.26	1	0	0.00012	-3.92	60% aq. PEG 400	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67: 211-221
9	N-N-diethyl m-toluamide	human	191.28	10.70	2.26	1	0	0.000105	-3.98	75% aq. PEG 400	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67: 211-221
10	N-N-diethyl m-toluamide	human	191.28	10.70	2.26	1	0	0.00121	-2.92	30% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52: 119-135
11	N-N-diethyl m-toluamide	human	191.28	10.70	2.26	1	0	0.0004	-3.40	60% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52: 119-135
12	N-N-diethyl m-toluamide	human	191.28	10.70	2.26	1	0	0.000016	-4.80	90% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52: 119-135
13	benzene	human	78.12	9.19	1.99	0	0	0.11	-0.95	water	isol. epidermis	abdomen	static	0.1% NaCL solution	31 (skin)	4	HPLC	*J.Invest.Dermatol.*, 85: 522-526
14	benzene	human	78.12	9.19	1.99	0	0	0.00094	-3.03	hexodecane	isol. epidermis	abdomen	static	0.1% NaCL solution	31 (skin)	0	HPLC	*J.Invest.Dermatol.*, 85: 522-526
15	benzene	human	78.12	9.19	1.99	0	0	0.1665	-0.78	isoctane	isol. epidermis	abdomen	static	0.1% NaCL solution	31 (skin)	0	HPLC	*J.Invest.Dermatol.*, 85: 522-526
16	benzene	human	78.12	9.19	1.99	0	0	0.0024	-2.62	isoctane	isol. epidermis	abdomen	static	0.1% NaCL solution	31 (skin)	0	HPLC	*J.Invest.Dermatol.*, 85: 522-526
17	benzene	human	78.12	9.19	1.99	0	0	0.00011	-3.96	isoctane	isol. epidermis	abdomen	static	0.1% NaCL solution	31 (skin)	0	HPLC	*J.Invest.Dermatol.*, 85: 522-526
18	mannitol	human	182.17	18.63	-3.01	6	6	0.000011	-4.96	dist. water	full-thickness	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (14C)	*Toxicol.Vitro*, 8: 827-830
19	mannitol	human	182.17	18.63	-3.01	6	6	0.000011	-4.96	dist. water	isol. epidermis	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (14C)	*Toxicol.Vitro*, 8: 827-830
20	mannitol	human	182.17	18.63	-3.01	6	6	0.000025	-4.60	dist. water	isol. epidermis	abdomen	flow-through	0.9% physiological saline	32	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 827-830
21	mannitol	human	182.17	18.63	-3.01	6	6	0.000025	-4.60	dist. water	dermat. 0.13 mm	abdomen	flow-through	0.9% physiological saline	not available	not available	radiolabelled (14C)	*Toxicol.Vitro*, 8: 827-830
22	water	human	18.02	26.68	-1.38	1	1	0.000754	-3.12	saline	full-thickness	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8: 827-830
23	water	human	18.02	26.68	-1.38	1	1	0.000689	-3.16	saline	isol. epidermis	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8: 827-830
24	water	human	18.02	26.68	-1.38	1	1	0.00091	-3.04	saline	isol.epidermis	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8: 827-830
25	water	human	18.02	26.68	-1.38	1	1	0.00118	-2.93	saline	dermatomed 0.13 mm	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8: 827-830
26	water	human	18.02	26.68	-1.38	1	1	0.000707	-3.15	saline	dermatomed 0.13 mm	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8: 827-830

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
27	erioglaucine	human	793.86	not calc.	-1.5	not calc.	not calc.	0.00000136	-5.87	40% propylene glycol	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol*, 42: 468-472
28	erioglaucine	human	793.86	not calc.	-1.5	not calc.	not calc.	0.00000306	-5.51	propylene glycol & dodecylazacyclo-heptan-2-one	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol*, 42: 468-472
29	erioglaucine	human	793.86	not calc.	-1.5	not calc.	not calc.	0.0000026	-5.59	propylene glycol & 5% dimethylsulphoxide	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol*, 42: 468-472
30	erioglaucine	human	793.86	not calc.	-1.5	not calc.	not calc.	0.00000338	-5.47	propylene glycol & sodium lauryl sulphate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol*, 42: 468-472
31	erioglaucine	human	793.86	not calc.	-1.5	not calc.	not calc.	0.00000282	-5.55	propylene glycol & dodecyl-L-pyroglutamate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol*, 42: 468-472
32	testosterone	human	288.4	10.66	3.27	2	1	0.005012	-2.30	0.05M phosphate buffer 20% ethanol	dermatom. 0.41 mm	abdomen / breast	static	0.05M phosphate buffer	32 (skin)	28	radiolabelled (14C)	*Eur.J.Pharm. Sci*, 11: 59-68
33	water	human	18.02	26.68	-1.38	1	1	0.00171	-2.77	none	dermatomed skin	abdomen	static	0.9% saline	30 (not available)	not available	radiolabelled (3H)	*J.Pharm.Pharmacol*, 36: 261-262
34	androstedione	human	288.42	10.03	2.75	2	0	0.00124	-2.91	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11): 2270-2273
35	ethinyl estradiol	human	296.4	12.04	4	2	1	0.0000374	-4.43	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11): 2270-2273
36	prednisone	human	358.44	12.71	1.46	5	2	0.0000246	-4.61	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11): 2270-2273
37	prednisolone	human	360.44	12.96	1.49	5	3	0.0000235	-4.63	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11): 2270-2273
38	betamethasone	human	392.45	12.37	2.02	6	3	0.000002	-5.70	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11): 2270-2273
39	b-estradiol	human	272.4	11.90	3.94	2	2	0.01	-2.00	5% oleic acid, in 75% ethanol	dermatomed 0.5 mm	abdomen	static	5% oleic acid, in 75% ethanol	32	60	radiolabelled (3H)	*Pharm.Res.*, 10: 1745-1750
40	chlorpyrifos	human	350.59	10.10	4.66	1	0	0.00025	-3.60	commercial solution containing xylene & 111-TCE	full-thickness	breast	flow-through	50% aq.ethanol	32 (skin)	24	gas chromatography	*Hum.Exp.Toxicol*, 19: 104-107
41	DEHP	human	390.57	9.39	8.39	2	0	0.0000057	-5.24	none	isol.epidermis	abdomen	static	50% aq.ethanol	30 (not available)	72	radiolabelled (14C)	*Environ.Health Perspect.*, 74: 223-227
42	DEP	human	222.24	10.51	2.65	2	0	0.0000114	-4.94	none	isol.epidermis	abdomen	static	50% aq.ethanol	30 (not available)	30	radiolabelled (14C)	*Environ.Health Perspect.*, 74: 223-227
43	dibutylphthalate	human	278.35	10.86	5.11	2	0	0.0000023	-5.64	none	isol.epidermis	abdomen	static	50% aq.ethanol	30 (not available)	30	radiolabelled (14C)	*Environ.Health Perspect.*, 74: 223-227
44	lindane	human	290.83	8.54	4.26	0	0	0.0000059	-5.23	acetone	dermat. 0.23 mm	breast / abdomen	static	50% aq.ethanol	32 (skin)	6	gas chromatography	*Hum.Exp.Toxicol.*, 16: 652-657
45	lindane	human	290.83	8.54	4.26	0	0	0.0000059	-5.23	acetone	dermat. 0.23 mm	breast / abdomen	static	50% aq.ethanol	32 (skin)	24	gas chromatography	*Hum.Exp.Toxicol.*, 16: 652-657
46	chlorpyrifos	human	350.59	10.10	4.66	1	0	0.00011	-3.96	ethanol	full-thickness	breast	flow-through	50% aq.ethanol	32(skin)	24	gas chromatography	*Hum.Exp.Toxicol*, 19: 104-107
47	nonane	human	128.3	7.51	4.76	0	0	0.000042	-4.38	JP-8	dermatom.0.5 6 mm	back	static	6% Volpo20 in PBS	32 (skin)	4	GC	*Toxicol. Sci*, 55: 247-255
48	b-estradiol	human	272.4	11.90	3.94	2	2	0.001	-3.00	75% ethanol	dermatomed 0.5 mm	abdomen	static	75% ethanol	32	60	radiolabelled (3H)	*Pharm.Res.*, 10: 1745-1750
49	aldosterone	human	360.45	12.31	1.63	4	2	3.00E-06	-5.52	water	isol. epidermis	not given	static	aq. penecillin / streptomycin	26 (not available)	not available	radiolabelled	*J.Invest.Dermatol*, 52: 63-70
50	b-estradiol	human	272.4	11.90	3.94	2	2	0.0003	-3.52	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52: 63-70
51	estriol	human	288.4	12.95	2.81	3	3	0.00004	-4.40	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52: 63-70
52	estrone	human	270.4	11.55	3.43	2	1	0.0036	-2.44	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52: 63-70
53	hydrocortisone	human	362.5	12.75	1.61	5	3	0.000003	-5.52	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled	*J.Investig.Dermatol.*, 52: 63-70

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
54	pregnenolone	human	316.5	10.36	3.89	2	1	0.0015	-2.82	water	is. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol*, 52: 63-70
55	progesterone	human	314.5	10.05	3.67	2	0	0.0015	-2.82	water	is. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol*, 52: 63-70
56	testosterone	human	288.4	10.66	3.27	2	1	0.0004	-3.40	water	is. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled	*J.Invest.Dermatol.*, 49: 5S2
57	cortexolone	human	346.47	11.91	3.15	4	2	0.000075	-4.12	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52: 63-70
58	corticosterone	human	346.5	11.91	1.99	4	2	0.00006	-4.22	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52: 63-70
59	cortisone	human	360.5	12.1	1.81	5	2	0.00001	-5.00	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52: 63-70
60	adenosine	human	267.24	15.97	-1.05	9	4	0.000133	-3.88	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32(skin)	24	UV/VS	*Eur.J.Pharm.Sci.*, 2006
61	cimetidine	human	252.34	12.86	0.4	6	3	0.000038	-4.42	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32 (skin)	24	radiolabelled	*Eur.J.Pharm.Sci.*, 2006
62	deoxyadenosine	human	251.24	15.49	-0.55	8	3	0.000129	-3.89	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32 (skin)	24	UV/VS	*Eur.J.Pharm.Sci.*, 2006
63	methiocarb	human	225.31	10.92	2.87	1	1	0.0011	-2.96	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*, 48: 697-701
64	pirimicarb	human	238.29	11.05	1.4	4	0	0.0027	-2.57	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*, 48: 697-701
65	prochloraz	human	376.7	10.69	4.13	3	0	0.0007	-3.15	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*, 48: 697-701
66	dibutyl squarate	human	226.27	10.58	2.45	4	0	0.00002	-4.70	acetone	dermatomed skin	thigh	static	buffer	not given	48	UV spectroscopy	*Arch.Dermatol.Res.*, 280: 57-60
67	diethyl squarate	human	170.16	11.50	4.07	4	0	0.00012	-3.92	acetone	dermatomed skin	thigh	static	buffer	not available	48	UV spectroscopy	*Arch.Dermatol.Res.*, 280: 57-60
68	squaric acid	human	114.06	20.47	-0.44	4	2	0.0000075	-5.12	acetone	dermatom.	thigh	static	buffer	not available	48	UV spectroscopy	*Arch.Dermatol.Res.*, 280: 57-60
69	5-fluorouracil	human	130.01	13.46	-0.81	3	2	0.000601	-3.22	aq. buffered solution	epidermis	abdomen	static	buffered saline solution pH 7.4 + plysorbate 80	37	36	not available	*I.J.Pharmac.*, 129: 33-40
70	morphine	human	285.3	13.68	0.72	4	2	0.0000093	-5.03	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	52	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6: 825-832
71	sufentanil	human	386.6	10.47	3.62	3	0	0.012	-1.92	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	8.5	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6: 825-832
72	codeine	human	299.4	12.09	1.28	4	1	0.000049	-4.31	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	24	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6: 825-832
73	fentanyl	human	336.5	10.30	3.89	2	0	0.0056	-2.25	physiological buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	9	GCL with nitrogen selective detector	*Pharmaceut.Res.*, 6: 825-832
74	hydromorphone	human	285.34	10.96	1.6	4	1	0.000015	-4.82	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	56	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6: 825-832
75	meperidine	human	247.4	9.82	3.03	2	0	0.0037	-2.43	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	8	GLC with nitrogen selective detector	*Pharmaceut.Res.* 6: 825-832
76	testosterone	human	288.4	10.66	3.27	2	1	0.00012	-3.92	ethanol	full-thickness	abdomen	static	culture medium & 10% BSA	32	22	radiolabelled (14C)	*J.Control.Release*, 76: 327-335
77	propoxur	human	209.25	10.31	1.9	2	1	0.000885	-3.05	60% aq. ethanol	full-thickness	abdomen	static	culture medium & 10% fetal bovine serum	32	24	radiolabelled (14C)	*Toxicol.Sci*, 58: 15-22
78	thymol	human	150.2	10.81	3.52	1	1	0.0528	-1.28	dist. water	is. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29: 677-683
79	4-bromophenol	human	173.01	11.48	2.4	1	1	0.03612	-1.44	dist. water	is. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29: 677-683
80	2-butoxyethanol	human	118.18	9.88	0.57	2	1	0.000214	-3.67	None	is. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57: 193-197
81	2-(2-butoxyethoxy) ethanol	human	162.23	9.74	0.29	3	1	0.0000357	-4.45	None	is. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57: 193-197

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
82	chloroxylenol	human	156.6	11.20	3.25	1	1	0.05904	-1.23	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol*, 29: 677-683
83	2-cresol (o-cresol)	human	108.1	11.89	2.06	1	1	0.01572	-1.80	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol*, 29: 677-683
84	3-cresol (m-cresol)	human	108.14	11.89	2.06	1	1	0.01524	-1.82	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol*, 29: 677-683
85	4-cresol (p-cresol)	human	108.1	11.89	2.06	1	1	0.01752	-1.76	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol*, 29: 677-683
86	2-ethoxyethanol	human	90.12	10.33	-0.42	2	1	0.000842	-3.07	none	full-thickness	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect*., 57: 193-197
87	2-(2-ethoxyethoxy) ethanol	human	134.18	10.04	-0.69	3	1	0.000132	-3.88	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect*., 57: 193-197
88	2-ethoxyethyl acetate	human	132.16	9.22	0.59	2	0	0.000807	-3.09	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect*., 57: 193-197
89	2-methoxyethanol	human	76.10	10.67	-0.91	2	1	0.00289	-2.54	none	is. epidermis	abdomen	static	dist. water	30(not available)	8	GC with flame ionisation	*Environ.Health Perspect*, 57: 193-197
90	2-(2-ethoxyethoxy) ethanol	human	120.15	10.25	-1.18	3	1	0.000206	-3.69	none	isol. epidermis	abdomen	static	dist. water	30(not available)	8	GC with flame ionisation	*Environ.Health Perspect*, 57: 193-197
91	1-methoxylpropan-2-ol	human	90.12	10.16	-0.49	2	1	0.00125	-2.90	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation detection	*Environ.Health. Perspect*, 57: 193-197
92	2-naphthol	human	144.16	12.69	2.69	1	1	0.0279	-1.55	dist. water	isol. epidermis	abdomen	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol*, 29: 677-683
93	3-nitrophenol	human	139.1	13.02	1.91	2	1	0.00564	-2.25	dist. water	isol. epidermis	abdomen	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol*, 29: 677-683
94	phenol	human	94.11	12.33	1.51	1	1	0.00822	-2.09	dist. water	is. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol*, 29: 677-683
95	resorcinol	human	110.11	15.18	1.03	2	2	0.00024	-3.62	dist. water	is. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol*, 29: 677-683
96	3,4 xylenol	human	202.55	11.54	2.61	1	1	0.036	-1.44	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol*., 29: 677-683
97	2-phenylphenol	human	170.21	12.24	3.28	1	1	0.00159	-2.80	60% aq. ethanol	full-thickness	abdomen	static	Dulbecco's MEM, HEPES: Ham F-12, glutamx-I, BSA, L-glutamine, hydrocortisone & gentamycin	32	8	radiolabelled (14C)	*Regul.Toxicol.Pharmacol.*, 35: 198-208
98	hydroquinone	human	110.11	15.18	1.03	2	2	9.33E-06	-5.03	not available	isol. epidermis	abdomen	static	Dulbecco's PBS, antibiotics and fungicides	30	8	radiolabelled (14C)	*Food Chem.Toxicol*., 35: 1009-1016
99	testosterone	human	288.4	10.66	3.27	2	1	0.0000267	-4.57	ethanol	dermatom. 0.28 mm	breast	flow-through	Eagles MEM & 2% PEG (pH 7.4)	32 (not available)	24	radiolabelled (14C)	*Toxicology*, 168: 63
100	1-methoxylpropan-2-ol	human	90.12	10.16	-0.49	2	1	0.00144	-2.84	water	dermatom. 0.5 mm	breast	flow-through	Eagles MEM & sodium carbonate & gentamycin	32	24	radiolabelled (14C)	*Int.Arch.Occup.Environ.Health*, 75: 519-527
101	1-methoxylpropan-2-ol	human	90.12	10.16	-0.49	2	1	0.000065	-4.19	none	dermatom. 0.5 mm	breast	flow-through	Eagles MEM & sodium carbonate & gentamycin	32	24	radiolabelled (14C)	*Int.Arch.Occup.Environ.Health*, 75: 519-527
102	1-methoxylpropan-2-ol	human	90.12	10.16	-0.49	2	1	0.00065	-3.19	none	dermatom. 0.5 mm	breast	flow-through	Eagles MEM & sodium carbonate & gentamycin	32	24	radiolabelled (14C)	*Int.Arch.Occup.Environ.Health*, 75: 519-527
103	parathion	human	291.26	10.76	3.73	1	0	0.000189	-3.72	none	dermatom. 0.5 mm	back	flow-through	Eagles-MEM-BSS & gentamycin	37	96	radiolabelled	*Toxicol.Appl.Pharmacol.*, 168: 149-152
104	triclosan	human	289.55	10.02	2.47	2	1	0.000034	-4.47	methanol and adhesive Durotak 387-2051	isol. epidermis	breast and abdomen	static	ethanol & PBS	37	12	HPLC	*Int.J.Pharm.*, 235: 229-236
105	DDT	human	354.49	9.45	6.79	0	0	0.00594	-2.23	acetone	dermatomed 0.5 mm	abdomen	flow-through	Hanks HEPES buffered medium, 4% BSA & gentamycin	37	48	radiolabelled (14C)	*Toxicol. Vitro*, 8: 1225-1232
106	bisphenol A diglycidyl ether (BADGE)	human	340.8	10.38	3.84	4	0	4.80E-07	-6.32	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
107	o-cresyl glycidyl ether (oCGE)	human	164.2	10.38	2.16	2	0	9.30E-05	-4.03	acetone	dermatommed	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
108	dodecyl glycidyl ether (C12GE)	human	242.2	8.41	5.01	2	0	0.00000331	-5.48	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
109	epikote YX4000	human	354.4	11.00	5.19	4	0	0.000000047	-7.33	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
110	1,6-hexanediol diglycidyl ether (HDDGE)	human	230.2	9.36	0.84	4	0	0.000136	-3.87	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
111	2,4 dimethylamine	human	266.13	9.52	0.84	3	2	0.000945	-3.02	commercial formulation clean crop	dermatom.0.3 mm	abdomen	flow-through	HBSS, HEPES, buffer BSA & gentamycin sulphate	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 11: 251-262
112	2,4 dimethylamine	human	266.13	9.52	0.84	3	2	0.00081	-3.09	commercial formulation Wilbur Ellis	dermatom.0.3 mm	abdomen	flow-through	HBSS, HEPES, buffer BSA & gentamycin sulphate	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 11: 251-262
113	coumarin	human	146.15	11.91	1.51	1	0	0.000376	-3.42	ethanol	full-thickness	breast	flow-through	HEPES buffered HBSS & 0.5% gentamycin	32 (skin)	72	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.*, 145: 34-42
114	coumarin	human	146.15	11.91	1.51	1	0	0.000719	-3.14	ethanol	full-thickness	breast	flow-through	HEPES buffered HBSS & 0.5% gentamycin	32 (skin)	72	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.*, 145: 34-42
115	cannabinol	human	310.46	10.9	7.23	2	1	0.00015	-3.82	propylene glycol: water (7:3) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol*, 56: 291-297
116	cannabidiol	human	314.46	11.11	8.01	2	2	0.00024	-3.62	propylene glycol: water (7:3) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol*, 56: 291-297
117	Δ-tetrahydrocan-nabinol (THC)	human	314.46	9.75	7.6	2	1	0.000028	-4.55	propylene glycol: water: ethanol (9:1:1) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol*, 56: 291-297
118	benzyl nicotinate	human	213.24	11.55	2.35	2	0	0.016	-1.80	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci*, 80: 54-56
119	benzyl nicotinate	human	213.24	11.55	2.35	2	0	2.04 E-05	-4.69	none	isol. epidermis		static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci*, 80: 54-56
120	butyl nicotinate	human	179.22	10.57	2.11	2	0	0.0166	-1.78	water	is. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37 (not available)	5	HPLC	*J.Pharm.Sci.*, 80: 54-56
121	butyl nicotinate	human	179.22	10.57	2.11	2	0	0.000079	-4.10	none	is. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37 (not available)	5	HPLC	*J.Pharm.Sci.*, 80: 54-56
122	ethyl nicotinate	human	151.17	11.06	1.13	2	2	0.00608	-2.22	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37(not available)	5	HPLC	*J.Pharm.Sci*, 80: 54-56
123	ethyl nicotinate	human	151.17	11.06	1.13	2	2	0.0066	-2.18	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37(not available)	5	HPLC	*J.Pharm.Sci*, 80: 54-56
124	ethyl nicotinate	human	151.17	11.06	1.13	2	2	0.000216	-3.65	none	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37 (not available)	5	HPLC	*J.Pharm.Sci*, 80: 54-56
125	n-hexyl nicotinate	human	207.27	10.49	3.1	2	0	0.0179	-1.75	water	is. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*, 80: 54-56
126	n-hexyl nicotinate	human	207.27	10.49	3.1	2	0	1.22E-05	-4.91	none	is. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*, 80: 54-56
127	methyl nicotinate	human	137.14	11.80	0.64	2	0	0.00309	-2.51	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*, 80: 54-56
128	methyl nicotinate	human	137.14	11.80	0.64	2	0	0.0034	-2.47	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*, 80: 54-56
129	nicotinic acid	human	123.11	13.23	0.69	2	1	0.000024	-4.62	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci*, 80: 104-107
130	naltrexone (NTX)	human	341	13.75	1.39	5	2	0.0095	-2.02	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci*, 91: 2571-2578
131	NTX-3-acetate (ACE-NTX)	human	383	12.96	1.47	5	1	0.0077	-2.11	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci*, 91: 2571-2578
132	NTX-3-propionate (PROP-NTX)	human	397	12.06	1.96	5	1	0.0025	-2.60	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci*, 91: 2571-2578
133	NTX-3-butyrate (BUT-NTX)	human	411	11.88	2.45	5	1	0.0013	-2.89	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci*, 91: 2571-2578
134	NTX-3-valerate (VAL-NTX)	human	425	11.72	2.45	5	1	0.0007	-3.15	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci*, 91: 2571-2578
135	NTX-3-hexanoate (HEX-NTX)	human	439	11.57	2.94	5	1	0.0012	-2.92	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci*, 91: 2571-2578

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
136	NTX-3 heptanoate (HEP-NTX)	human	453	11.44	3.92	5	1	0.0009	-3.05	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	J.Pharm.Sci, 91: 2571-2578
137	etodolac	human	287.26	10.86	3.93	3	2	0.00746	-2.13	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Science*, 92:3: 656-664
138	ketoprofen	human	254.29	11.75	3.12	2	1	0.00062	-3.21	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Science*, 92:3: 656-664
139	nimesulide	human	308.31	15.25	2.22	3	2	0.00101	-3.00	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Science*, 92:3: 656-664
140	nizatidine	human	331.45	12.36	-0.43	5	2	0.000038	-4.43	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Science*, 92:3: 656-664
141	ranitidine	human	314.1	11.41	0.29	5	2	0.0000887	-4.05	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Science*, 92:3: 656-664
142	etorphine	human	411.55	11.76	3.02	5	2	0.0036	-2.44	HCL & isotonic TRIS buffer	full-thickness	abdominal	static	isotonic TRIS buffer	37	24	radiolabelled (3H)	*Pharm.Res.*, 9: 963-965
143	2-phenoxyethanol	human	138.17	11.49	1.1	2	1	0.001337	-2.87	methanol	dermat. 0.33	breast / abdomen / leg	flow-through	MEM & penicillin / streptomycin +CO2	37	6	HPLC	*Food Chem.Toxicol*, 35: 1009-1016
144	salicylic acid	human	138.1	14.39	2.24	2	2	0.00133	-2.88	not available	dermatom. 0.5 mm	breast	static	MEM, Ham's F-12, sodium bicarbonate, HEPES & gentamycin sulphate	37	12	radiolabelled (14C)	*J.Toxicol.: Cutaneous Ocul.Toxicol*, 12: 129-138
145	salicylic acid	human	138.1	14.39	2.24	2	2	0.00133	-2.88	not available	dermat. 0.5 mm	abdomen	static	MEM, Ham's F-12, sodium bicarbonate, HEPES & gentamycin sulphate	37	12	radiolabelled (14C)	*J.Toxicol.: Cutaneous Ocul.Toxicol*, 12: 129-138
146	2-ethoxyethanol	human	90.12	10.33	-0.42	2	1	0.000059	-4.23	methanol	dermat. 0.28 mm	breast	flow-through	MEM, sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl.Pharmacol*., 180: 74-82
147	2-ethoxyethanol	human	90.12	10.33	-0.42	2	1	0.000074	-4.13	methanol	dermat. 0.28 mm	breast	flow-through	MEM, sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl.Pharmacol*., 180: 74-82
148	bisoprolol	human	325.5	10.01	1.84	5	2	0.00027	-3.57	Sorensen's phosphate buffer (pH7.4)	dermatom. 1.2 mm	abdominal	flow-through	normal saline	32	72	HPLC	*Int.J.Pharm.*, 173: 141-148
149	celiprolol	human	379.5	11.51	1.93	5	3	0.00059	-3.23	Sorensen's phosphate buffer (pH7.4)	dermatom. 1.2 mm	abdominal	flow-through	normal saline	32	72	HPLC	*Int.J.Pharm.*, 173: 141-148
150	theophylline	human	180.17	14.05	-0.39	4	1	0.000432	-3.36	water	dermatomed 0.2 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*, 40: 231-242
151	methyl-4-hydroxy benzoate	human	152.14	12.50	2	2	1	0.000025	-4.60	PEG 400	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*, 40: 231-242
152	methyl-4-hydroxy benzoate	human	152.14	12.50	2	2	1	0.00032	-3.49	propylene glycol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*, 40: 231-242
153	methyl-4-hydroxy benzoate	human	152.14	12.50	2	2	1	0.000287	-3.54	1-propanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*, 40: 231-242
154	methyl-4-hydroxy benzoate	human	152.14	12.50	2	2	1	0.00054	-3.27	ethanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*, 40: 231-242
155	methyl-4-hydroxy benzoate	human	152.14	12.50	2	2	1	0.00295	-2.53	methanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*, 40: 231-242
156	methyl-4-hydroxy benzoate	human	152.14	12.50	2	2	1	0.00417	-2.38	water	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*, 40: 231-242
157	methyl-4-hydroxy benzoate	human	152.14	12.50	2	2	1	0.00478	-2.32	water	dermatom. 0.32 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*, 40: 231-242
158	aldosterone	human	360.45	12.31	1.63	4	2	5.80E-05	-4.24	not available	isol. epidermis	various	static	not available	26 (not available)	not available	radiolabelled	*J.Pharm.Sci*, 84: 1144-1146
159	b-estradiol	human	272.4	11.90	3.94	2	2	0.0041	-2.39	water	isol. epidermis	various	static	not available	37	not available	radiolabelled (3H)	*J.Pharm.Sci*, 84: 1144-1146
160	progesterone	human	314.5	10.05	3.67	2	0	0.03	-1.52	not available	is. epidermis	various	static	not available	37 (not available)	not available	radiolabelled (14C)	*J.Pharm. Sci*, 84: 1144-1146
161	benzoic acid	human	122.1	11.94	1.87	1	1	0.025	-1.60	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*, 170: 129-133
162	benzoic acid	human	122.1	11.94	1.87	1	1	0.00133	-2.88	deionised water	dermatomed 0.6 mm	not available	flow-through	PBS	37	48	radiolabelled (14C)	*J.Pharm.Sci*, 85: 249-252

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
163	borax	human	201.22	not calc.	not calc.	0	0	0.00017	-3.77	water	dermatom.0.5 mm	thigh	flow-through	PBS	32 (skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*, 45: 42-51
164	boric acid	human	61.83	44.06	-0.22	3	3	0.00029	-3.54	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32 (skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*, 45: 42-51
165	boric acid	human	61.83	44.06	-0.22	3	3	0.0000014	-5.85	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32 (skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*, 45: 42-51
166	boric acid	human	61.83	44.06	-0.22	3	3	0.00012	-3.92	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32 (skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*, 45: 42-51
167	boric acid	human	61.83	44.06	-0.22	3	3	0.0005	-3.30	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32 (skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*, 45: 42-51
168	butyl paraben	human	194.23	11.45	3.47	2	1	0.0277	-1.56	deionised water	epidermis	abdomen	static	PBS	23	4	HPLC	*Eur.J.Pharm. Sci*, 21: 337-345
169	butyl paraben	human	194.23	11.45	3.47	2	1	0.056	-1.25	deionised water	epidermis	abdomen	static	PBS	30	4	HPLC	*Eur.J.Pharm. Sci*, 21: 337-345
170	butyl paraben	human	194.23	11.45	3.47	2	1	0.0996	-1.00	deionised water	epidermis	abdomen	static	PBS	37	4	HPLC	*Eur.J.Pharm. Sci*, 21: 337-345
171	butyl paraben	human	194.23	11.45	3.47	2	1	0.275	-0.56	deionised water	epidermis	abdomen	static	PBS	45	4	HPLC	*Eur.J.Pharm. Sci*, 21: 337-345
172	caffeine	human	194.2	32.83	0.16	4	0	0.000258	-3.59	water	is. epidermis	upper leg	static	PBS	37	24	HPLC	*Int.J.Pharm.*, 182: 41-47
173	dichlofenac	human	296.16	11.13	4.02	2	2	0.001	-3.00	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*, 170: 129-133
174	glyphosate	human	169.10	12.73	-4.47	3	4	0.000459	-3.34	water	dermatom. 1mm	not available	flow-through	PBS	37	24	radiolabelled (14C)	*Food Chem.Toxicol*, 34: 731-735
175	ibuprofen	human	206.3	10.21	3.79	1	1	0.0363	-1.44	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*, 170: 129-133
176	malathion	human	330.36	10.61	2.29	2	0	0.203	-0.69	aq. ethanol	dermat. 1mm	not available	flow-through	PBS	37	24	radiolabelled (14C)	*Food Chem.Toxicol*, 34: 731-735
177	methyl nicotinate	human	137.14	11.80	0.64	2	0	0.00389	-2.41	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*, 170: 129-133
178	methyl paraben	human	152.15	12.5	2	2	1	0.00418	-2.38	deionised water	epidermis	abdomen	static	PBS	23	4	HPLC	*Eur.J.Pharm. Sci*, 21: 337-345
179	methyl paraben	human	152.15	12.5	2	2	1	0.00943	-2.03	deionised water	epidermis	abdomen	static	PBS	30	4	HPLC	*Eur.J.Pharm. Sci*, 21: 337-345
180	methyl paraben	human	152.15	12.5	2	2	1	0.0213	-1.67	deionised water	epidermis	abdomen	static	PBS	37	4	HPLC	*Eur.J.Pharm. Sci*, 21: 337-345
181	methyl paraben	human	152.15	12.5	2	2	1	0.032	-1.49	deionised water	epidermis	abdomen	static	PBS	45	4	HPLC	*Eur.J.Pharm. Sci*, 21: 337-345
182	naproxene	human	230.3	11.42	3.1	2	1	0.00288	-2.54	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*, 170: 129-133
183	nicotine	human	162.3	11.25	1	2	0	0.00331	-2.48	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*, 170: 129-133
184	n-nitrosodiethanola-mine	human	134.13	15.67	-1.28	4	2	0.0041	-2.39	isoprpyl myristate + sucrose (3H)	isol.epidermis	abdomen	static	PBS	32 (skin)	48	radiolabelled (14C)	*Food Chem.Toxicol.*, 33: 315-322
185	salicylic acid	human	138.1	14.39	2.24	2	2	0.0138	-1.86	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*, 170: 129-133
186	testosterone	human	288.4	10.66	3.27	2	1	0.0002399	-3.62	deionised	dermatom. 0.6 mm	not available	flow-through	PBS	27	48	radiolabelled (14C)	*J.Pharm.Sci*, 85: 249-252
187	doxycycline HCL	human	444.44	16.55	-1.36	9	6	0.00000477	-5.32	ethanol	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
188	doxycycline HCL	human	444.44	16.55	-1.36	9	6	0.000211	-3.68	2:1 ethanol: M840	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
189	doxycycline HCL	human	444.44	16.55	-1.36	9	6	0.000266	-3.58	1:1 ethanol: M840	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
190	doxycycline HCL	human	444.44	16.55	-1.36	9	6	0.00253	-2.60	2:1 ethanol: M840	epidermis	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
191	doxycycline HCL	human	444.44	16.55	-1.36	9	6	0.00252	-2.60	1:1 ethanol: M840	epidermis	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
192	clotrimazole	human	344.85	11.17	6.26	2	0	0.002	-2.70	propylene glycol	dermatom. 0.6 mm	abdomen	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215: 51-56
193	hydrocortisone	human	362.5	12.75	1.61	5	3	0.0023	-2.64	propylene glycol	dermat. 0.6 mm	abdomen	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm*, 215: 51-56
194	salicylic acid	human	138.1	14.39	2.24	2	2	2.19	0.34	90% aq. propylene glycol	dermatom. 0.6 mm	abdomen	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215: 51-56
195	terbinafine	human	291.4	9.33	5.81	1	0	0.001	-3.00	propylene glycol	dermatomed 0.6 mm	abdomen	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm*, 215: 51-56
196	ITF 296	human	238	12.91	not calc.	3	0	0.00356	-2.45	water: propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS: propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm. Sci*, 11: 59-68
197	isosorbide dinitrate (ISDN)	human	236.14	10.36	0.76	4	0	0.00449	-2.35	water: propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS: propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm. Sci*, 11: 59-68
198	nicorandil	human	211.18	14.40	0.43	3	1	0.00005	-4.30	water: propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS: propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm. Sci*, 11: 59-68
199	griseofulvin	human	352.77	10.44	1.92	6	0	0.0013	-2.89	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp. Clin. Pharmacol*, 11: 643-646
200	griseofulvin	human	352.77	10.44	1.92	6	0	0.00194	-2.71	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled(3H)	*Meth. and Find Exp. Clin. Pharmacol*, 11: 643-646
201	salicylic acid	human	138.1	14.39	2.24	2	2	0.0131	-1.89	phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm. Sci*, 11: 59-68
202	coumarin	human	146.15	11.91	1.51	1	0	0.0091	-2.04	phosphate buffer (pH 7.4)	full-thickness	abdomen	static	phosphate buffer (pH 7.4)	37	48	radiolabelled (14C)	*Meth. and Find Exp. Clin. Pharmacol.*, 11: 643-646
203	coumarin	human	146.15	11.91	1.51	1	0	0.0125	-1.90	phosphate buffer (pH 7.4)	full-thickness	scalp	static	phosphate buffer (pH 7.4)	37	48	radiolabelled (14C)	*Meth. and Find Exp. Clin. Pharmacol.*, 11: 643-646
204	linoleic acid	human	289.45	9.05	7.51	1	1	0.0000106	-4.97	ethanol	full-thickness	abdomen	static	phosphate buffer, pluronic F88 & BHT	37	95	radiolabelled (14C)	*J.Pharm.Pharmacol*, 34: 610-611
205	dimethylformamide	human	73.1	10.63	-0.93	1	0	0.0096	-2.02	none	full-thickness	abdomen	flow-through	physiological solution	37	4	gas chromatography	*Occup. Hygiene*, 1: 191-198
206	2-ethoxyethanol	human	90.12	10.33	-0.42	2	1	0.000882	-3.05	none	full-thickness	abdomen	flow-through	physiological solution	37	4	gas chromatography	*Occup.Hygiene*, 1: 191-198
207	propoxur	human	209.25	10.31	1.9	2	1	0.0000288	-4.54	aq. methanol	full-thickness	abdomen	static	RPMI, L-glutamine, gentamycin & 10% foetal calf serum	37	22	radiolabelled (14C)	*Toxicol. Appl. Pharmacol.*, 123: 144-150
208	propoxur	human	209.25	10.31	1.9	2	1	0.0407	-1.39	aq. methanol	full-thickness	abdomen	static	RPMI, L-glutamine, gentamycin & 10% foetal calf serum	37	22	radiolabelled (14C)	*Toxicol. Appl. Pharmacol.*, 123: 144-150
209	caffeine	human	194.2	32.83	0.16	4	0	0.00072	-3.14	petrolatum	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol*, 115: 1-11
210	caffeine	human	194.2	32.83	0.16	4	0	0.00062	-7.39	petrolatum	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol*, 115: 1-11
211	caffeine	human	194.2	32.83	0.16	4	0	0.00021	-3.68	ethylene glycol	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol*, 115: 1-11
212	caffeine	human	194.2	32.83	0.16	4	0	0.00051	-3.29	water gel	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol*, 115: 1-11
213	ethanol	human	46.07	10.92	-0.14	1	1	0.000317	-3.50	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol.*, 96: 921-925
214	mannitol	human	182.17	18.63	-3.01	6	6	0.000061	-4.21	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol.*, 96: 921-925
215	methotrexate	human	454.45	15.05	-1.28	10	5	0.000318	-3.50	50% aq. propylene glycol	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int. J.Pharm.*, 25: 65-75
216	methotrexate	human	454.45	15.05	-1.28	10	5	0.000113	-3.95	0.03M HCL % aq. propylene glycol (pH 1.98)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int. J.Pharm.*, 25: 65-75
217	methotrexate	human	454.45	15.05	-1.28	10	5	0.000562	-3.25	0.001M KOH, 50% aq. propylene glycol (pH 4.12)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int. J.Pharm.*, 25: 65-75

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
218	methotrexate	human	454.45	15.05	-1.28	10	5	0.00113	-2.95	0.01M KOH, 50% aq. propylene glycol (pH 5.29)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int. J.Pharm.*, 25: 65-75
219	methotrexate	human	454.45	15.05	-1.28	10	5	0.00052	-3.28	0.05 M KOH, 50% aq. propylene glycol (pH 6.34)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int. J.Pharm.*, 25: 65-75
220	nicorandil	human	211.18	14.40	0.43	3	1	0.000266	-3.58	water	full-thickness	breast	static	saline	37	32	HPLC	*J.Pharm.Sci*, 7: 231-236
221	testosterone	human	288.4	10.66	3.27	2	1	0.00028	-3.55	petrolatum	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115: 1-11
222	testosterone	human	288.4	10.66	3.27	2	1	0.00018	-3.74	ethylene glycol	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115: 1-11
223	testosterone	human	288.4	10.66	3.27	2	1	0.00671	-2.17	water gel	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115: 1-11
224	2-phenylphenol	human	170.21	12.24	3.28	1	1	0.0266	-1.58	60% aq. ethanol	is. epidermis	dorsal / flank	static	saline (0.9% NaCL), 0.01% sodium azide & 3% BSA	32	8	radiolabelled (14C)	*Regul.Toxicol.Pharmacol.*, 35: 198-208
225	2-phenylphenol	human	170.21	12.24	3.28	1	1	0.0183	-1.74	60% aq. ethanol	is. epidermis	abdomen	static	saline (0.9% NaCL), 0.01% sodium azide & 3% BSA	32	8	radiolabelled (14C)	*Regul.Toxicol.Pharmacol.*, 35: 198-208
226	nikel	human	58.7	0	-0.57	0	0	0.00061	-3.21	synthetic sweat pH 6.5	full-thickness	abdomen	static	saline solution 0.9% NaCl	32 (skin)	24	electrothermal spectrometry	*Toxicology Letters* 170 (2007): 49-56
227	aniline	human	93	10.83	1.08	1	1	6.10E-02	-1.21	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.*, 129: 33-40
228	4-n-butylaniline	human	149.24	9.51	3.1	1	1	0.411	-0.39	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.*, 129: 33-40
229	ethylaniline	human	121.2	9.73	2.11	1	1	0.288	-0.54	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.*, 129: 33-40
230	4-n-pentylaniline	human	163.3	9.79	3.59	1	1	0.226	-0.65	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.*, 129: 33-40
231	2-phenylethanol	human	122.2	11.38	1.57	1	1	0.031	-1.51	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.*, 129: 33-40
232	4-phenylbutanol	human	150	10.80	2.55	1	1	0.0862	-1.06	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.*, 129: 33-40
233	lidocaine	human	234.34	8.78	1.66	2	1	0.000344	-3.46	40% propylene glycol & HCL (pH4)	dermat. 0.15 mm	leg	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (14C)	*Int. J.Pharm.*, 71: 167-173
234	lidocaine	human	234.34	8.78	1.66	2	1	0.000388	-3.41	40% propylene glycol & HCL (pH6)	dermat. 0.15 mm	leg	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (14C)	*Int. J.Pharm.*, 71: 167-173
235	lidocaine	human	234.34	8.78	1.66	2	1	0.0106	-1.97	40% propylene glycol & HCL (pH10)	dermat. 0.15 mm	leg	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (14C)	*Int. J.Pharm.*, 71: 167-173
236	methyl parathion	human	263.21	10.45	2.75	1	0	0.000013	-4.87	acetone	full-thickness	abdomen	static	saline, 4% BSA & gentamycin sulphate	32 (skin)	48	gas chromatography	*Occup.Environ.Med.*, 54: 524-525
237	methyl parathion	human	263.21	10.45	2.75	1	0	0.000038	-4.42	20% MPA, 75% xylene, 5% dispersing agents	full-thickness	abdomen	static	saline, 4% BSA & gentamycin sulphate	32 (skin)	48	gas chromatography	*Occup.Environ.Med.*, 54: 524-525
238	hydrocortisone	human	362.5	12.75	1.61	5	3	0.000158	-3.80	Britton-Robinson 0.2M buffers & ethanol, pH1	full-thickness	abdomen	flow-through	solution of NaCl & sodium azide	37	28	HPLC	*J.Contr.Release*, 76: 327-335
239	hydrocortisone	human	362.5	12.75	1.61	5	3	0.000075	-4.12	Britton-Robinson 0.2M buffers & ethanol, pH6	full-thickness	abdomen	flow-through	solution of NaCl & sodium azide	37	28	HPLC	*J.Contr.Release*, 76: 327-335
240	hydrocortisone	human	362.5	12.75	1.61	5	3	0.000095	-4.02	Britton-Robinson 0.2M buffers & ethanol, pH10	full-thickness	abdomen	flow-through	solution of NaCl & sodium azide	37	28	HPLC	*J.Contr.Release*, 76: 327-335
241	testosterone	human	288.4	10.66	3.27	2	1	0.012	-1.92	0.1M phosphate buffer pH1	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
242	testosterone	human	288.4	10.66	3.27	2	1	0.0117	-1.93	0.1M phosphate buffer pH2	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
243	testosterone	human	288.4	10.66	3.27	2	1	0.00912	-2.04	hydrochloric acid and potassium chloride pH2	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
244	testosterone	human	288.4	10.66	3.27	2	1	0.012	-1.92	0.1M phosphate buffer pH6	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
245	testosterone	human	288.4	10.66	3.27	2	1	0.04	-1.40	0.1M phosphate buffer pH12	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
246	atenolol	human	266.3	12.49	-0.03	4	3	0.00005	-4.30	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
247	flufenamic acid	human	281.2	10.96	4.88	5	2	0.0005209	-3.28	wool alcohols ointment	sc 0.012 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel*, 75: 283-295
248	flufenamic acid	human	281.2	10.96	4.88	5	2	0.0005407	-3.27	wool alcohols ointment	sc 0.012 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel*, 75: 283-295
249	flufenamic acid	human	281.2	10.96	4.88	5	2	0.0003889	-3.41	wool alcohols ointment	sc 0.012 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel*, 75: 283-295
250	flufenamic acid	human	281.2	10.96	4.88	5	2	0.0005499	-3.26	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel*, 75: 283-295
251	flufenamic acid	human	281.2	10.96	4.88	5	2	0.0005107	-3.29	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel*, 75: 283-295
252	flufenamic acid	human	281.2	10.96	4.88	5	2	0.0003798	-3.42	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel*, 75: 283-295
253	flufenamic acid	human	281.2	10.96	4.88	5	2	0.0000397	-4.40	wool alcohols ointment	full-thickness	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel*, 75: 283-295
254	flufenamic acid	human	281.2	10.96	4.88	5	2	0.0000929	-4.03	wool alcohols ointment	full-thickness	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel*, 75: 283-295
255	flufenamic acid	human	281.2	10.96	4.88	5	2	0.0000371	-4.43	wool alcohols ointment	full-thickness	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel*, 75: 283-295
256	metoprolol	human	267.4	10.39	1.69	4	2	0.00083	-3.08	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
257	oxprenolol	human	265.4	10.52	1.83	4	2	0.00154	-2.81	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
258	propranolol	human	295.3	11.13	2.6	3	2	0.00178	-2.75	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
259	paraquat	human	257.16	10.45	-2.71	0	0	0.0000087	-5.06	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J. Investig.Dermatol*, 96: 921-925
260	diazinon	human	304.35	14.98	3.86	2	1	0.0095	-2.02	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile ringer's solution, Trizma, glucose	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 1219-1224
261	N-N-diethyl m-toluamide	human	191.28	10.70	2.26	1	0	0.00224	-2.65	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, Trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 7: 141-148
262	salicylic acid	human	138.1	14.39	2.24	2	2	0.01194	-1.92	0.1M phosphate buffer (pH2)	full-thickness	breast	static	tris.HCL buffer sol.	25	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418
263	salicylic acid	human	138.1	14.39	2.24	2	2	0.00074	-3.13	0.1M phosphate buffer (pH4)	full-thickness	breast	static	tris.HCL buffer sol.	25	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418
264	methanol	human	32.04	11.68	-0.84	1	1	0.0016	-2.80	water	stratum corneum	abdomen	static	water	22 (not available)	48	radiolabelled	*Int. J.Pharm.*, 18: 299-309
265	n-octanol	human	130.23	9.45	2.81	1	1	0.061	-1.21	water	strarum corneum	abdomen	static	water	22 (not available)	48	radiolabelled (14C)	*Int.J.Pharm.*, 18: 299-309
266	phenol	human	94.11	12.33	1.51	1	1	0.000149	-3.83	water	stratum corneum	abdomen	static	water	22 (not available)	10	UV spectrometry	*Int.J.Pharm.*.,18: 299-309
267	methyl paraben	human	152.15	12.5	2	2	1	0.00000589	-5.23	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci.*, 96, No.4, 2007
268	butyl paraben	human	194.23	11.45	3.47	2	1	0.000029	-4.54	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci.*, 96, No.4, 2007
269	atropine	pig	289.38	11.04	1.91	3	1	0.00000176	-5.75	isotonic phosphate buffered saline (pH7.4) with ethanol, propylene glycol, azone	epidermal membrane	pig ears	flow-through	PBS-buffer	37	24	radiolabelled (3H)	Bosman 1996.
270	mannitol	pig	182.17	18.63	-3.01	6	6	0.00152	-2.82	dist. water	isol. epidermis	outer ear	flow-through	physiological saline	32	not available	radiolabelled (14C)	*Toxicol.Vitro* 8: 827-830
271	2-phenylphenol	pig	170.21	12.24	3.28	1	1	0.0159	-1.80	60% aq. ethanol	full-thickness	ear	per-fused pig ear	oxygenated and filtered blood	30	4	radiolabelled (14C)	*Reg.Toxicol.Pharmacol.*, 35: 198-208

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
272	salicylic acid	pig	138.10	14.39	2.24	2	2	1.27	0.10	90% aq. propylene glycol	dermatomed 0.6 mm	unknown	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.* 215: 51-56
273	scopolamine	pig	303.40	11.53	0.39	4	1	0.00000051	-6.29	isotonic phosphate buffered saline (pH7.4) with ethanol, propylene glycol, azone	epidermal membrane	pig ears	flow-through	PBS-buffer	37	24	radiolabelled (3H)	Bosman 1996.
274	terbinafine	pig	291.4	9.33	5.81	1	0	0.001	-3.00	propylene glycol	dermatomed 0.6 mm	unknown	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215: 51-56
275	tropicamide	pig	284.40	12.53	1.19	3	1	0.0000007	-6.15	isotonic phosphate buffered saline (pH7.4) with ethanol, propylene glycol, azone	epidermal membrane	pig ears	flow-through	PBS-buffer	37	24	radiolabelled (3H)	Bosman 1996.
276	water	pig	18.02	26.68	-1.38	1	1	0.00225	-2.65	saline	full-thickness	outer ear	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro* 8: 827-830
277	caprtopril	pig	217.29	11.55	0.84	2	2	0.000297	-3.53	aq. saturated sol.	fresh epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
278	caprtopril	pig	217.29	11.55	0.84	2	2	0.00147	-2.83	aq. saturated sol.	frozen epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
279	methyl ester	pig	231.29	9.31	2.9	2	0	0.001276	-2.75	aq. saturated sol.	fresh epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
280	methyl ester	pig	231.29	9.31	2.9	2	0	0.00359	-2.44	aq. saturated sol.	frozen epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
281	ethyl ester	pig	245.29	9.25	3.39	2	0	0.022	-1.66	aq. saturated sol.	fresh epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
282	ethyl ester	pig	245.29	9.25	3.39	2	0	0.0081	-2.09	aq. saturated sol.	frozen epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
283	propyl ester	pig	259	9.20	3.89	2	0	0.0158	-1.8	aq. saturated sol.	fresh epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
284	propyl ester	pig	259	9.20	3.89	2	0	0.0122	-1.91	aq. saturated sol.	frozen epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
285	butyl ester	pig	273.29	8.14	4.38	2	0	0.0146	-1.84	aq. saturated sol.	fresh epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
286	butyl ester	pig	273.29	8.14	4.38	2	0	0.0108	-1.97	aq. saturated sol.	frozen epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
287	pentyl ester	pig	287.29	9.11	4.87	2	0	0.00689	-2.16	aq. saturated sol.	fresh epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
288	pentyl ester	pig	287.29	9.11	4.87	2	0	0.00108	-2.97	aq. saturated sol.	frozen epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
289	hexyl ester	pig	301.29	9.07	5.36	2	0	0.00122	-2.91	aq. saturated sol.	frozen epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
290	ligustrazine hydrochloride	pig	136.1	10.24	2.18	2	0	0.0002363	-3.63	enhancer sol. with ethanol	sc	back	static	water	32	24	HPLC	*Eur.J.Pharm.Biopharm.*, 2007
291	ligustrazine hydrochloride	pig	136.1	10.24	2.18	2	0	0.000272	-3.57	enhancer sol. with azone	sc	back	static	water	32	24	HPLC	*Eur.J.Pharm.Biopharm.*, 2007
292	ligustrazine hydrochloride	pig	136.1	10.24	2.18	2	0	0.00287	-2.54	enhancer sol. with cinnamic acid	sc	back	static	water	32	24	HPLC	*Eur.J.Pharm.Biopharm.*, 2007
293	ligustrazine hydrochloride	pig	136.1	10.24	2.18	2	0	0.00173	-2.76	enhancer sol. with cinnamaldehyde	sc	back	static	water	32	24	HPLC	*Eur.J.Pharm.Biopharm.*, 2007
294	ligustrazine hydrochloride	pig	136.1	10.24	2.18	2	0	0.00169	-2.77	enhancer sol. with cinnamic alcohol	sc	back	static	water	32	24	HPLC	*Eur.J.Pharm.Biopharm.*, 2007

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
295	cafeic acid	pig	180.2	15.15	1.1	3	3	0.0016	-2.80	transcutol-propylene glycol	full-thickness	ears	static	isotonic saline solution, pH7	37	48	HPLC	*Int.J.Pharm.*, 331: 139-144
296	chlorogenic acid	pig	354.3	14.51	-1	7	6	0.0024	-2.62	transcutol-propylene glycol	full-thickness	ears	static	isotonic saline solution, pH7	37	48	HPLC	*Int.J.Pharm.*, 331: 139-144
297	pentachlorophenol	pig	266.33	10.78	5.12	1	1	0.00006	-4.22	ethanol	0.2-0.3 mm epidermal	dorsal	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007
298	pentachlorophenol	pig	266.33	10.78	5.12	1	1	0.00037	-3.43	water	0.2-0.3 mm epidermal	dorsal	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007
299	pentachlorophenol	pig	266.33	10.78	5.12	1	1	0.0048	-2.32	40% ethanol, 60% water	0.2-0.3 mm epidermal	dorsal	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007
300	pentachlorophenol	pig	266.33	10.78	5.12	1	1	0.0065	-2.19	40% ethanol, 60% water, MNA	0.2-0.3 mm epidermal	dorsal	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007
301	pentachlorophenol	pig	266.33	10.78	5.12	1	1	0.00009	-4.05	40% ethanol, 60% water, SLS	0.2-0.3 mm epidermal	dorsal	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007
302	ketoprofen	pig	254.29	11.75	0.97	2	1	0.00021	-3.68	water	epidermal membrane	ears	static	PBS (7.4)	37	48	HPLC	*Skin Pharmacol.Physiol* . 2010, 23: 113-116
303	ketoprofen	pig	254.29	11.75	0.97	2	1	0.000312	-3.51	aloe vera	epidermal membrane	ears	static	PBS (7.4)	37	48	HPLC	*Skin Pharmacol.Physiol* . 2010, 23: 113-116
304	benzoic acid	test skin	122.1	11.94	1.87	1	1	0.086	-1.07	water	3 micron pore size polycarbonate membrane	N/A	static	LDE Assay Medium	32	24	radiolabelled (14C)	*Toxicol. Vitro*, 6: 303-315
305	benzoic acid	test skin	122.1	11.94	1.87	1	1	0.0086	-2.07	water	3 micron pore size polycarbonate membrane	N/A	static	LDE Assay Medium	22	24	radiolabelled (14C)	*Toxicol. Vitro*, 6: 303-315
306	benzoic acid	test skin	122.1	11.94	1.87	1	1	0.0067	-2.17	petrolatum	3 micron pore size polycarbonate membrane	N/A	static	LDE Assay Medium	32	24	radiolabelled (14C)	*Toxicol. Vitro*, 6: 303-315
307	benzoic acid	test skin	122.1	11.94	1.87	1	1	0.0023	-2.64	petrolatum	3 micron pore size polycarbonate membrane	N/A	static	LDE Assay Medium	22	24	radiolabelled (14C)	*Toxicol. Vitro*, 6: 303-315
308	caffeine	test skin	194.2	32.83	0.16	4	0	0.02	-1.70	water	3 micron pore size polycarbonate membrane	N/A	static	LDE Assay Medium	32	24	radiolabelled (14C)	*Toxicol. Vitro*, 6: 303-315
309	caffeine	test skin	194.2	32.83	0.16	4	0	0.011	-1.96	water	3 micron pore size polycarbonate membrane	N/A	static	LDE Assay Medium	22	24	radiolabelled (14C)	*Toxicol. Vitro*, 6: 303-315
310	caffeine	test skin	194.2	32.83	0.16	4	0	0.0024	-2.62	petrolatum	3 micron pore size polycarbonate membrane	N/A	static	LDE Assay Medium	32	24	radiolabelled (14C)	*Toxicol. Vitro*, 6: 303-315
311	caffeine	test skin	194.2	32.83	0.16	4	0	0.0011	-2.96	petrolatum	3 micron pore size polycarbonate membrane	N/A	static	LDE Assay Medium	22	24	radiolabelled (14C)	*Toxicol. Vitro*, 6: 303-315
312	clotrimazole	graftskin	344.85	11.17	6.26	2	0	2.04	0.31	propylene glycol	support membrane was removed	N/A	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215: 51-56
313	clotrimazole	graftskin	344.85	11.17	6.26	2	0	1.88	0.27	propylene glycol	filter support was left attached	N/A	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215: 51-56
314	DDT	testskin	354.5	9.45	6.79	0	0	0.007	-2.15	acetone	full-thickness	cultured human forehead	flow-through	Hanks HEPES buffered medium, BSA & gentamycin	37	48	radiolabelled (14C)	*Toxicol. Vitro*, 8: 1219-1225
315	flufenamic acid	epiderm	281.2	10.96	4.88	5	2	0.002363	-2.62	wool alcohols ointment	pore size 0.00045 mm	N/A	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75: 283-295

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
316	flufenamic acid	epiderm	281.2	10.96	4.88	5	2	0.003053	-2.51	wool alcohols ointment	pore size 0.00045 mm	N/A	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75: 283-295
317	flufenamic acid	epiderm	281.2	10.96	4.88	5	2	0.002714	-2.57	wool alcohols ointment	pore size 0.00045 mm	N/A	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75: 283-295
318	salicylic acid	graftskin	138.1	14.39	2.24	2	2	4.55	0.66	90% aq. propylene glycol	support membrane was removed	N/A	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215: 51-56
319	salicylic acid	skinethic	138.1	14.39	2.24	2	2	15.28	1.18	90% aq. propylene glycol	filter support was left attached	N/A	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215: 51-56
320	terbinafine	graftskin	291.4	9.33	5.81	1	0	0.028	-1.56	propylene glycol	support membrane was removed	N/A	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215: 51-56
321	terbinafine	skinethic	291.4	9.33	5.81	1	0	0.037	-1.43	propylene glycol	filter support was left attached	N/A	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215: 51-56
322	testosterone	testskin	288.4	10.66	3.27	2	1	0.029	-1.54	water	3 micron pore size polycarbonate membrane	N/A	static	LDE assay medium & gentamycin sulphate	32	6	radiolabelled (14C)	*Skin Pharmacol.*, 5: 146-153
323	testosterone	testskin	288.4	10.66	3.27	2	1	0.014	-1.85	water	3 micron pore size polycarbonate membrane	N/A	static	LDE assay Medium & gentamycin sulphate	22	6	radiolabelled (14C)	*Skin Pharmacol* ., 5: 146-153
324	testosterone	testskin	288.4	10.66	3.27	2	1	0.0007	-3.15	petrolatum	3 micron pore size polycarbonate membrane	N/A	static	LDE Assay medium & gentamycin sulphate	22	6	radiolabelled (14C)	*Skin Pharmacol.*, 5: 146-154
325	testosterone	testskin	288.4	10.66	3.27	2	1	0.0016	-2.80	petrolatum	3 micron pore size polycarbonate membrane	N/A	static	LDE assay medium & gentamycin sulphate	32	6	radiolabelled (14C)	*Skin Pharmacol.*, 5: 146-154
326	amethocaine	silastic	264.37	9.85	3.02	3	1	0.00000149	-5.82	saturated solution of local anesthetic	5*10-3 cm thickness	N/A	static	saline	37	24	UV-spectroscopy	*Prediction of Perc.Penetration*, 1: 192-198
327	procaine	silastic	236.31	10.34	1.99	3	1	0.000000114	-6.94	saturated solution of local anesthetic	5*10-3 cm thickness	N/A	static	saline	37	24	UV-spectroscopy	*Prediction of Perc.Penetration*, 1: 192-198
328	benzocaine	silastic	165.19	11.11	1.8	2	1	0.00000135	-5.87	saturated solution of local anesthetic	5*10-3 cm thickness	N/A	static	saline	37	24	UV-spectroscopy	*Prediction of Perc.Penetration*, 1: 192-198
329	dibucaine	silastic	343.47	10.7	4.04	4	1	0.000000631	-6.19	saturated solution of local anesthetic	5*10-3 cm thickness	N/A	static	saline	37	24	UV-spectroscopy	*Prediction of Perc.Penetration*, 1: 192-198
330	ketocaine	silastic	291.43	9.38	3.6	2	0	0.00000034	-6.47	saturated solution of local anesthetic	5*10-3 cm thickness	N/A	static	saline	37	24	UV-spectroscopy	*Prediction of Perc.Penetration*, 1: 192-198
331	captopril	silastic	217.29	11.55	0.84	2	2	0.00394	-2.4	aq. saturated sol.	not available	N/A	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
332	methyl ester	silastic	231.29	9.31	2.9	2	0	0.00488	-2.31	aq. saturated sol.	not available	N/A	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
333	ethyl ester	silastic	245.29	9.25	3.39	2	0	0.00986	-2	aq. saturated sol.	not available	N/A	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
334	propyl ester	silastic	259	9.20	3.89	2	0	0.0222	-1.65	aq. saturated sol.	not available	N/A	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
335	butyl ester	silastic	273.29	8.14	4.38	2	0	0.0411	-1.39	aq. saturated sol.	not available	N/A	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
336	pentyl ester	silastic	287.29	9.11	4.87	2	0	0.0675	-1.17	aq. saturated sol.	not available	N/A	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*,. 58: 167-177
337	hexyl ester	silastic	301.29	9.07	5.36	2	0	0.107	-0.91	aq. saturated sol.	not available	N/A	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
338	pentachlorophenol	silastic	266.33	10.78	5.12	1	1	0.014	-1.85	ethanol	0.25 mm	N/A	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007
339	pentachlorophenol	silastic	266.33	10.78	5.12	1	1	0.029	-1.54	water	0.25 mm	N/A	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
340	pentachlorophenol	silastic	266.33	10.78	5.12	1	1	0.01	-2	40% ethanol, 60% water	0.25 mm	N/A	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007
341	pentachlorophenol	silastic	266.33	10.78	5.12	1	1	0.012	-1.92	40% ethanol, 60% water, MNA	0.25 mm	N/A	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007
342	pentachlorophenol	silastic	266.33	10.78	5.12	1	1	0.005	-2.30	40% ethanol, 60% water, SLS	0.25 mm	N/A	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007
343	alachlor	mouse	269.77	9.80	3.37	2	0	0.000377	-3.42	diluted acetone with water (1:10)	full-thickness	dorsal	flow-through	Hanks balanced salne solution & 4% BSA	not available	24	radiolabelled (14C)	*Toxicol.Sciences*, 68: 18-23
344	alachlor	mouse	269.77	9.80	3.37	2	0	0.000655	-3.18	diluted acetone with water (1:40)	full-thickness	dorsal	flow-through	Hanks balanced salne solution & 4% BSA	not available	24	radiolabelled (14C)	*Toxicol.Sciences*, 68: 18-23
345	atenolol	mouse	266.3	12.49	-0.03	4	3	0.048	-1.32	methanol	full-thickness	abdomen	flow-through	0.1 % sodium azide solution in dist. water	37	24	UV-spectroscopy	*Ind.J.Exp.Biol.*, 31: 691-693
346	atenolol	mouse	266.3	12.49	-0.03	4	3	0.0479	-1.32	methanol	full-thickness	dorsal	flow-through	0.1 % sodium azide solution in dist. water	37	24	UV-spectroscopy	*Ind.J.Exp.Biol.*, 31: 691-693
347	atenolol	mouse	266.3	12.49	-0.03	4	3	0.0301	-1.52	methanol	full-thickness	abdomen	flow-through	0.1 % sodium azide solution in dist. water	37	24	UV-spectroscopy	*Ind.J.Exp.Biol.*, 31: 691-693
348	atenolol	mouse	266.3	12.49	-0.03	4	3	0.025	-1.60	methanol	full-thickness	dorsal	flow-through	0.1 % sodium azide solution in dist. water	37	24	UV-spectroscopy	*Ind.J.Exp.Biol.*, 31: 691-693
349	atenolol	mouse	266.3	12.49	-0.03	4	3	0.0351	-1.45	methanol	full-thickness	abdomen	flow-through	0.1 % sodium azide solution in dist. water	37	24	UV-spectroscopy	*Ind.J.Exp.Biol.*, 31: 691-693
350	atenolol	mouse	266.3	12.49	-0.03	4	3	0.0213	-1.67	methanol	full-thickness	dorsal	flow-through	0.1 % sodium azide solution in dist. water	37	24	UV-spectroscopy	*Ind.J.Exp.Biol.*, 31: 691-693
351	atrazine	mouse	215.69	11.77	2.82	5	2	0.000769	-3.11	diluted methanol with water (1:10)	full-thickness	dorsal	flow-through	Hanks balanced salne solution & 4% BSA	not available	24	radiolabelled (14C)	*Toxicol.Sci*, 68: 18-23
352	atrazine	mouse	215.69	11.77	2.82	5	2	0.000168	-3.77	diluted methanol with water (1:40)	full-thickness	dorsal	flow-through	Hanks balanced salne solution & 4% BSA	not available	24	radiolabelled (14C)	*Toxicol.Sci*, 68: 18-23
353	bisphenol A diglycidyl ether (BADGE)	mouse	340.8	10.38	3.84	4	0	0.0000085	-5.07	acetone	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	not available	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
354	n-butanol	mouse	74.14	10.13	0.84	1	1	0.0065	-2.19	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	0.3	radiolabelled (14C)	*J.Invest.Dermatol.*75: 346-352
355	n-butanol	mouse	74.14	10.13	0.84	1	1	0.0082	-2.09	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	4.3	radiolabelled (14C)	*J.Invest.Dermatol.*75: 346-352
356	n-butanol	mouse	74.14	10.13	0.84	1	1	0.0118	-1.93	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	7.8	radiolabelled (14C)	*J.Invest.Dermatol.*75: 346-352
357	n-butanol	mouse	74.14	10.13	0.84	1	1	0.0124	-1.91	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	11.3	radiolabelled (14C)	*J.Invest.Dermatol.*75: 346-352
358	n-butanol	mouse	74.14	10.13	0.84	1	1	0.0119	-1.92	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	14.3	radiolabelled (14C)	*J.Invest.Dermatol.*75: 346-352
359	n-butanol	mouse	74.14	10.13	0.84	1	1	0.0115	-1.94	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	26.3	radiolabelled (14C)	*J.Invest.Dermatol.*75: 346-352
360	n-butanol	mouse	74.14	10.13	0.84	1	1	0.0127	-1.90	saline & (3H) methanol	full-thickness	abdomen	static	saline	not available	2	radiolabelled (14C)	*J.Soc.Cosmet.*, 35: 237-252
361	n-butanol	mouse	74.14	10.13	0.84	1	1	0.0237	-1.63	saline & (3H) methanol	full-thickness	back	static	saline	not available	2	radiolabelled (14C)	*J.Soc.Cosmet.*, 35: 237-252
362	caffeine	mouse	194.2	32.83	0.16	4	0	0.00026	-3.59	isotonic phosphate buffer	full-thickness	dorsal / abdominal	static	isotonic phosphate buffer & sodium azide	37	9	HPLC	*J.Cont.Release*, 33: 71-77
363	corticosterone	mouse	346.5	11.91	1.99	4	2	0.00053	-3.28	40% aq. PEG 400	full-thickness	abdomen	static	40% aq. PEG 400	37	not available	HPLC	*J.Pharm.Sci.*, 76: 123-126
364	coumarin	mouse	146.15	11.91	1.51	1	0	0.001	-3.00	ethanol	full-thickness	dorsal	flow-through	HBSS, HEPES & 0.5% gentamycin	32 (skin)	72	radiolabelled (14C)	*Toxicol.Appl.Pharmacol*, 145: 34-42
365	o-cresyl glycidyl ether (oCGE)	mouse	164.20	10.38	2.16	2	0	0.000176	-3.75	acetone	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
366	decabromodiphenyl oxide (DBDPO)	mouse	959.17	12.11	8.10	1	0	0.00000117	-5.93	tetrahydrofuran	full-thickness	dorsal	flow-through	HEPES-buffered HBSS & 10% FBS	not available	24	radiolabelled (14C)	*Food Chem.Toxicol*, 39: 1263

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
367	decabromodiphenyl oxide (DBDPO)	mouse	959.17	12.11	8.10	1	0	0.00000164	-5.79	tetrahydrofuran	full-thickness	dorsal	flow-through	HEPES-buffered HBSS & 10% FBS	not available	24	radiolabelled (14C)	*Food Chem.Toxicol*, 39: 1263
368	decabromodiphenyl oxide (DBDPO)	mouse	959.17	12.11	8.10	1	0	0.00000703	-5.15	tetrahydrofuran	full-thickness	dorsal	flow-through	HEPES-buffered HBSS & 10% FBS	not available	24	radiolabelled (14C)	*Food Chem.Toxicol*, 39: 1263
369	deoxycortisone	mouse	330.47	11.03	3.12	3	1	0.0034	-2.47	40% aq. PEG 400	full-thickness	abdomen	static	40% aq. PEG 400	37	not available	HPLC	*J.Pharm.Sci*., 76: 123-126
370	dibutyl squarate	mouse	226.27	10.58	2.45	4	0	0.00085	-3.07	acetone	full-thickness	not available	static	not available	not available	48	UV-spectroscopy	*Arch.Dermatol.Res.*, 280: 57-60
371	diethyl squarate	mouse	170.16	11.50	4.07	4	0	0.001	-3.00	acetone	full-thickness	not available	static	not available	not available	48	UV-spectroscopy	*Arch.Dermatol.Res.*, 280: 57-60
372	dodecyl glycidyl ether (C12GE)	mouse	242.2	8.41	5.01	2	0	4.61E-05	-4.34	acetone	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
373	ethanol	mouse	46.07	10.92	-0.14	1	1	0.0021	-2.68	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	0.5	radiolabelled (14C)	*J.Invest.Dermatol*., 75: 346-352
374	ethanol	mouse	46.07	10.92	-0.14	1	1	0.0022	-2.66	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	5.5	radiolabelled (14C)	*J.Invest.Dermatol*., 75: 346-352
375	ethanol	mouse	46.07	10.92	-0.14	1	1	0.0023	-2.64	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	10.5	radiolabelled (14C)	*J.Invest.Dermatol*., 75: 346-352
376	ethanol	mouse	46.07	10.92	-0.14	1	1	0.0022	2.66	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	15.5	radiolabelled (14C)	*J.Invest.Dermatol*., 75: 346-352
377	ethanol	mouse	46.07	10.92	-0.14	1	1	0.0021	-2.68	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	20.5	radiolabelled (14C)	*J.Invest.Dermatol*., 75: 346-352
378	ethanol	mouse	46.07	10.92	-0.14	1	1	0.002	-2.70	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	25.5	radiolabelled (14C)	*J.Invest.Dermatol*., 75: 346-352
379	ethanol	mouse	46.07	10.92	-0.14	1	1	0.0019	-2.72	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	29.5	radiolabelled (14C)	*J.Invest.Dermatol*., 75: 346-352
380	ethanol	mouse	46.07	10.92	-0.14	1	1	0.0009	-3.05	saline & (3H) water	full-thickness	abdomen	static	saline	not available	2	radiolabelled (14C)	*J.Soc.Cosmet*., 35: 237-252
381	ethanol	mouse	46.07	10.92	-0.14	1	1	0.0024	-2.62	saline & (3H) water	full-thickness	back	static	saline	not available	2	radiolabelled (14C)	*J.Soc.Cosmet*., 35: 237-252
382	epikote YX4000	mouse	354.4	11.00	5.19	4	0	2.63 E -06	-5.58	acetone	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
383	erioglaucine	mouse	793.86	not calc.	-1.5	notcalc.	not calc.	0.00003	-4.52	40% propylene glycol & 10% N-Methyl-2-pyrrolidone	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol*., 42: 468-472
384	etorphine	mouse	411.55	11.76	3.02	5	2	0.0046	-2.34	HCL & isotonic TRIS buffer	full-thickness	abdominal / dorsal	static	isotonic tris buffer	37	24	radiolabelled (3H)	*Pharmaceut.Res*., 9: 963-965
385	5-fluorouracil	mouse	130.01	13.46	-0.81	3	2	0.0000603	-4.22	0.002% aq. sodium azide solution	dermatomed 0.42 mm	abdomen	flow-through	0.002% aq. sodium azide solution	31	24	radiolabelled (3H)	*J.Investig.Pharmacol*., 94: 235-240
386	n-hexanol	mouse	102.18	9.71	2.03	1	1	0.0194	-1.71	0.9% saline	full-thickness	abdomen	static	saline	not available	0.5	radiolabelled (14C)	*J.Investig.Dermatol*., 75: 346-352
387	n-hexanol	mouse	102.18	9.71	2.03	1	1	0.0286	-1.54	0.9% saline	full-thickness	abdomen	static	saline	not available	5	radiolabelled (14C)	*J.Investig.Dermatol*., 75: 346-352
388	n-hexanol	mouse	102.18	9.71	2.03	1	1	0.0386	-1.41	0.9% saline	full-thickness	abdomen	static	saline	not available	10	radiolabelled (14C)	*J.Investig.Dermatol*., 75: 346-352
389	n-hexanol	mouse	102.18	9.71	2.03	1	1	0.0374	-1.43	0.9% saline	full-thickness	abdomen	static	saline	not available	15	radiolabelled (14C)	*J.Investig.Dermatol*., 75: 346-352
390	n-hexanol	mouse	102.18	9.71	2.03	1	1	0.0374	-1.43	0.9% saline	full-thickness	abdomen	static	saline	not available	20	radiolabelled (14C)	*J.Investig.Dermatol*., 75: 346-352
391	n-hexanol	mouse	102.18	9.71	2.03	1	1	0.00381	-2.42	0.9% saline	full-thickness	abdomen	static	saline	not available	28	radiolabelled (14C)	*J.Investig.Dermatol*., 75: 346-352
392	n-hexanol	mouse	102.18	9.71	2.03	1	1	0.0845	-1.07	saline & (3H) methanol	full-thickness	back	static	saline	not available	2	radiolabelled (14C)	*J.Soc.Cosmet*., 35: 237-252
393	1,6-hexanediol diglycidyl ether (HDDGE)	mouse	230.2	9.36	0.84	4	0	5.77 E -04	-3.24	acetone	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
394	n-heptanol	mouse	116.2	9.57	1.82	1	1	0.0659	-1.18	0.9% saline	full-thickness	abdomen	static	saline	not available	0.5	radiolabelled (14C)	*J.Investig.Dermatol.*, 75: 346-352
395	n-heptanol	mouse	116.2	9.57	1.82	1	1	0.0807	-1.09	0.9% saline	full-thickness	abdomen	static	saline	not available	5	radiolabelled (14C)	*J.Investig.Dermatol*, 75: 346-352
396	n-heptanol	mouse	116.2	9.57	1.82	1	1	0.1014	-0.99	0.9% saline	full-thickness	abdomen	static	saline	not available	10	radiolabelled (14C)	*J.Investig.Dermatol*, 75: 346-352
397	n-heptanol	mouse	116.2	9.57	1.82	1	1	0.0979	-1.01	0.9% saline	full-thickness	abdomen	static	saline	not available	15	radiolabelled (14C)	*J.Investig.Dermatol*, 75: 346-352
398	n-heptanol	mouse	116.2	9.57	1.82	1	1	0.1026	-0.98	0.9% saline	full-thickness	abdomen	static	saline	not available	20	radiolabelled (14C)	*J.Investig.Dermatol*, 75: 346-352
399	n-heptanol	mouse	116.2	9.57	1.82	1	1	0.1015	-0.99	0.9% saline	full-thickness	abdomen	static	saline	not available	25	radiolabelled (14C)	*J.Investig.Dermatol*, 75: 346-352
400	hydrocortisone	mouse	362.5	12.75	1.62	5	3	0.0001	-4.00	saline	full-thickness	abdomen	static	saline	37	40	radiolabelled (3H)	*J.Pharm.Sci.*, 73: 1287-1290
401	hydrocortisone	mouse	362.5	12.75	1.62	5	3	0.00012	-3.92	saline	full-thickness	dorsal	static	saline	37	40	radiolabelled (3H)	*J.Pharm.Sci.*, 73: 1287-1290
402	hydrocortisone	mouse	362.5	12.75	1.62	5	3	0.00006	-4.22	40% aq. PEG 400	full-thickness	abdomen	static	40% aq. PEG 400	37	not available	HPLC	*J.Pharm.Sci.*, 76: 123-126
403	17a-hydroxyproge-sterone	mouse	330.5	10.98	3.08	3	1	0.00087	-3.06	40% aq. PEG 400	full-thickness	abdomen	static	40% aq. PEG 400	37	not available	HPLC	*J.Pharm.Sci.*, 76: 123-126
404	lidocaine	mouse	234.34	8.78	1.66	2	1	0.0089	-2.05	40% propylene glycol & HCL	full-thickness	dorsal / ventral	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (14C)	*Int.J.Pharm.*, 71: 167-173
405	lidocaine	mouse	234.34	8.78	1.66	2	1	0.0176	-1.75	40% propylene glycol & HCL	full-thickness	dorsal / ventral	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (14C)	*Int.J.Pharm.*, 71: 167-173
406	lidocaine	mouse	234.34	8.78	1.66	2	1	0.018	-1.74	40% propylene glycol & NaOH	full-thickness	dorsal / ventral	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (14C)	*Int.J.Pharm.*, 71: 167-173
407	lidocaine	mouse	234.34	8.78	1.66	2	1	0.026	-1.59	40% propylene glycol & NaOH	full-thickness	dorsal / ventral	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (14C)	*Int.J.Pharm.*, 71: 167-173
408	N-N-diethyl m-toluamide	mouse	191.28	10.70	2.26	1	0	0.0035	-2.46	acetone	full-thickness	back	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 7: 167-176
409	methanol	mouse	32.04	11.68	-0.63	1	1	0.0018	-2.74	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	0.3	radiolabelled (14C)	*J.Investig.Dermatol.*, 75: 346-352
410	methanol	mouse	32.04	11.68	-0.63	1	1	0.0016	-2.80	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	5.8	radiolabelled (14C)	*J.Investig.Dermatol.*, 75: 346-352
411	methanol	mouse	32.04	11.68	-0.63	1	1	0.0017	-2.77	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	9.8	radiolabelled (14C)	*J.Investig.Dermatol.*, 75: 346-352
412	methanol	mouse	32.04	11.68	-0.63	1	1	0.0019	-2.72	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	13.8	radiolabelled (14C)	*J.Investig.Dermatol.*, 75: 346-352
413	methanol	mouse	32.04	11.68	-0.63	1	1	0.0018	-2.74	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	17.8	radiolabelled (14C)	*J.Investig.Dermatol.*, 75: 346-352
414	methanol	mouse	32.04	11.68	-0.63	1	1	0.0018	-2.74	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	26.3	radiolabelled (14C)	*J.Investig.Dermatol.*, 75: 346-352
415	methanol	mouse	32.04	11.68	-0.63	1	1	0.001	-3.00	saline & (14C) alkanol	full-thickness	abdomen	static	saline	not available	2	radiolabelled (3H)	*J.Soc.Cosmet.Chem.*, 35: 237-252
416	morphine	mouse	285.3	13.68	0.72	4	2	0.00015	-3.82	isotonic phosphate buffer	full-thickness	dorsal / abdominal	flow-through	isotonic phosphate buffer & sodium azide	37	9	HPLC	*Int.J.Pharm.*, 299: 131-137
417	nicorandil	mouse	211.18	14.40	0.43	3	1	0.001008	-3.00	water	full-thickness	abdomen	static	saline	37	32	HPLC	*J.Pharm.Sci*, 80: 104-107
418	n-octanol	mouse	130.23	9.45	2.81	1	1	0.0782	-1.11	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	0.8	radiolabelled (14C)	*J.Investig.Dermatol.*,75: 346-352
419	n-octanol	mouse	130.23	9.45	2.81	1	1	0.1208	-0.92	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	6.2	radiolabelled (14C)	*J.Investig.Dermatol.*,75: 346-352
420	n-octanol	mouse	130.23	9.45	2.81	1	1	0.0945	-1.02	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	10	radiolabelled (14C)	*J.Investig.Dermatol.*,75: 346-352
421	n-octanol	mouse	130.23	9.45	2.81	1	1	0.0931	-1.03	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	15	radiolabelled (14C)	*J.Investig.Dermatol.*,75: 346-352

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
422	n-octanol	mouse	130.23	9.45	2.81	1	1	0.0948	-1.02	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	22	radiolabelled (14C)	*J.Investig.Dermatol.*,75: 346-352
423	n-octanol	mouse	130.23	9.45	2.81	1	1	0.097	-1.01	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	27	radiolabelled (14C)	*J.Investig.Dermatol.*,75: 346-352
424	prednisolone 21-heptanoate	mouse	472.62	12.02	4.6	5	2	0.000077	-4.11	DES / ethanol	not available	abdomen	not available	ethanol & water (8:2)	25 (not available)	48	HPLC	*Int.J.Pharm.*, 158: 11-18
425	prednisolone 21-octanoate	mouse	486.65	11.89	5.09	5	2	0.00011	-3.96	DES / ethanol	not available	abdomen	not available	ethanol & water (8:2)	25 (not available)	48	HPLC	*Int.J.Pharm.*, 158: 11-18
426	prednisolone 21-nonanoate	mouse	500.68	11.78	5.58	5	2	0.000092	-4.04	DES / ethanol	not available	abdomen	not available	ethanol & water (8:2)	25 (not available)	48	HPLC	*Int.J.Pharm.*, 158: 11-18
427	prednisolone 21-decanoate	mouse	514.7	11.67	6.07	5	2	0.000111	-3.95	DES / ethanol	not available	abdomen	not available	ethanol & water (8:2)	25 (not available)	48	HPLC	*Int.J.Pharm.*, 158: 11-18
428	prednisolone 21-undecanoate	mouse	528.73	11.57	5.54	5	2	0.000149	-3.83	DES / ethanol	not available	abdomen	not available	ethanol & water (8:2)	25 (not available)	48	HPLC	*Int.J.Pharm.*, 158: 11-18
429	prednisolone 21-tridecanoate	mouse	556.78	11.39	6.02	5	2	0.000106	-3.97	DES / ethanol	not available	abdomen	not available	ethanol & water (8:2)	25 (not available)	48	HPLC	*Int.J.Pharm.*, 158: 11-18
430	prednisolone 21-pentadecanoate	mouse	584.84	11.23	6.79	5	2	0.000098	-4.01	DES / ethanol	not available	abdomen	not available	ethanol & water (8:2)	25 (not available)	48	HPLC	*Int.J.Pharm.*, 158: 11-18
431	progesterone	mouse	314.5	10.05	3.67	2	0	0.011	-1.96	40% aq. PEG 400	full-thickness	abdomen	static	40% aq. PEG 400	37	not available	HPLC	*J.Pharm.Sci.*, 76: 123-126
432	propranolol HCL	mouse	295	11.96	0.74	3	2	0.00005	-4.30	hydroalcoholic mixture	full-thickness	abdomen	flow-through	dist. water	37	not available	HPLC	*J.Pharm.Sci*, 86: 1369-1372
433	salicylic acid	mouse	138.1	14.39	2.24	2	2	0.01954	-1.71	phosphate buffer	full-thickness	dorsal	static	tris HCL buffer sol.	25	72	Fluorescence, spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418
434	salicylic acid	mouse	138.1	14.39	2.24	2	2	0.01162	-1.93	citric acid phosphate	full-thickness	dorsal	static	tris HCL buffer sol.	25	72	Fluorescence, spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418
435	salicylic acid	mouse	138.1	14.39	2.24	2	2	0.00074	-3.13	citric acid phosphate	full-thickness	dorsal	static	tris HCL buffer sol.	25	72	Fluorescence, spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418
436	squaric acid	mouse	114.06	20.47	-0.44	4	2	0.0007	-3.15	acetone	full-thickness	not available	static	not available	not available	48	UV-spectroscopy	*Arch.Dermatol.Res.*, 280: 57-60
437	sucrose	mouse	342.3	18.06	-4.27	11	8	0.0022	-2.66	NS	full-thickness	not available	flow-through	isotonic PBS	37	not available	radiolabelled (3H)	*J.Pharm.Sci*, 90: 1242-1254
438	thiourea	mouse	76.12	15.23	-1.31	0	2	9.60E-05	-4.02	ethanol	full-thickness	abdomen	static	saline	37	6	radiolabelled (14C)	*Int.J.Pharm.*,36: 61-66
439	TDCPP	mouse	430.91	8.67	3.65	1	0	0.00046	-3.34	acetone	full-thickness	dorsal	flow-through	HEPES-buffered, HBSS & 10% FBS	not available	24	radiolabelled (14C)	*Food Chem.Toxicol.*, 39: 1263-1270
440	TDCPP	mouse	430.91	8.67	3.65	1	0	0.00056	-3.25	acetone	full-thickness	dorsal	flow-through	HEPES-buffered, HBSS &10% FBS	not available	24	radiolabelled (14C)	*Food Chem.Toxicol.*, 39: 1263-1270
441	trifluralin	mouse	335.28	9.49	5.31	6	0	0.000279	-3.55	diluted acetone with water (1:10)	full-thickness	dorsal	flow-through	Hanks balanced salne solution & 4% BSA	not available	24	radiolabelled (14C)	*Toxicol.Sci*, 68: 18-23
442	trifluralin	mouse	335.28	9.49	5.31	6	0	0.000122	-3.91	diluted acetone with water (1:40)	full-thickness	dorsal	flow-through	Hanks balanced salne solution & 4% BSA	not available	24	radiolabelled (14C)	*Toxicol.Sci*, 68: 18-23
443	water	mouse	18.02	26.68	-1.38	1	1	0.00219	-2.66	none	full-thickness	dorsal	flow-through	0.002% sodium azide solution	31 (skin)	6	radiolabelled (3H)	*J.Investig.Dermatol.*, 94: 235-240
444	water	mouse	18.02	26.68	-1.38	1	1	0.0016	-2.80	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	0.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
445	water	mouse	18.02	26.68	-1.38	1	1	0.0015	-2.82	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	5.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
446	water	mouse	18.02	26.68	-1.38	1	1	0.0014	-2.85	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	10.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
447	water	mouse	18.02	26.68	-1.38	1	1	0.0013	-2.89	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	15.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
448	water	mouse	18.02	26.68	-1.38	1	1	0.0012	-2.92	0.9% saline	full-thickness	abdomen / dorsal	static	saline	not available	25.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
449	water	mouse	18.02	26.68	-1.38	1	1	1.10E-05	-4.96	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not available	29.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
450	water	mouse	18.02	26.68	-1.38	1	1	2.95E-03	-2.53	none	full-thickness	not available	flow-through	PBS	35 (skin)	48	radiolabelled (3H)	*J.Investig.Dermatol.*, 93: 87-91
451	water	mouse	18.02	26.68	-1.38	1	1	1.90E-03	-2.72	saline (14C) ethanol	full-thickness	abdomen	static	saline	not available	2	radiolabelled (3H)	*J.Soc.Cosmet.Chem.*, 35: 237-252
452	water	mouse	18.02	26.68	-1.38	1	1	2.00E-02	-1.70	saline (14C) ethanol	full-thickness	back	static	saline	not available	2	radiolabelled (3H)	*J.Soc.Cosmet.Chem.*, 35: 237-252
453	water	mouse	18.02	26.68	-1.38	1	1	1.80E-02	-1.74	aq. urea	not available	dorsal	flow-through	saline & unlabelled urea	37 (not available)	48	radiolabelled (3H)	*S. African J. Sci.*, 84: 440-441
454	water	mouse	18.02	26.68	-1.38	1	1	1.00E-02	-2.00	aq. urea	not available	dorsal	flow-through	saline & unlabelled urea	37 (not available)	12	radiolabelled (3H)	*S. African J. Sci.*, 84: 440-441
455	urea	mouse	60.6	14.36	-1.56	1	2	3.00E-04	-3.52	water	not available	dorsal	flow-through	saline & unlabelled urea	37 (not available)	6	radiolabelled (3H)	*S. African J. Sci.*, 84: 440-441
456	urea	mouse	60.6	14.36	-1.56	1	2	7.00E-04	-3.15	water	not available	dorsal	flow-through	saline & unlabelled urea	37 (not available)	12	radiolabelled (3H)	*S. African J. Sci.*, 84: 440-441
457	alizapride	rat	339.9	12.06	1.8	6	2	0.0057	-2.24	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci*, 83: 29-32
458	aminopyrene	rat	231	10.7	0.6	3	0	0.033	-1.48	IPM	full-thickness	not available	static	ethanol	32	8	HPLC	*Int.J.Pharm*, 262: 13-22
459	aniline	rat	93	10.83	1.08	1	1	0.067	-1.17	physiological buffered solution	isol.epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100: 1-7
460	benzoic acid	rat	122.1	11.94	1.87	1	1	0.0286	-1.54	ethanol	isol.epidermis	back	flow-through	50% aq. ethanol	31.5 (skin)	30	radiolabelled (14C)	*Toxicol.Vitro*, 12: 47-55
461	benzoic acid	rat	122.1	11.94	1.87	1	1	0.00952	-2.02	ethanol	isol. epidermis	back	flow-through	PBS	31.5 (skin)	30	radiolabelled (14C)	*Toxicol.Vitro*, 12: 47-55
462	benzoic acid	rat	122.1	11.94	1.87	1	1	0.00035	-3.46	petrolatum	full-thickness	back	static	saline & thimerosol	32	not available	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.*, 62: 474-480
463	benzoic acid	rat	122.1	11.94	1.87	1	1	0.00029	-3.54	petrolatum	full-thickness	abdomen	static	saline & thimerosol	32	not available	radiolabelled (14C)	*J.Soc.Cosmet.Chem.*, 34: 127-135
464	benzyl acetate	rat	150.18	10.10	2.08	1	0	0.00027	-3.57	none	full-thickness	dorsal	flow-through	0.9% saline	32 (skin)	48	radiolabelled (14C)	*Food Chem.Toxicol.*, 28: 443-447
465	benzyl acetate	rat	150.18	10.10	2.08	1	0	0.000058	-4.24	50% aq. ethanol	full-thickness	dorsal	flow-through	0.9% saline	32 (skin)	48	radiolabelled (14C)	*Food Chem.Toxicol.*, 28: 443-447
466	bisphenol A diglycidyl ether (BADGE)	rat	340.8	10.38	3.84	4	0	5.50E-06	-5.26	acetone	dermatomed skin	dorsal	flow-through	HBSS, HEPES buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
467	bromopride	rat	344.26	10.74	1.94	4	2	0.0078	-2.11	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci*, 83: 29-32
468	bufexamac	rat	223.3	12.43	1.98	3	2	0.271	-0.57	IPM	full-thickness	not available	static	ethanol	32	8	HPLC	*Int.J.Pharm*, 262: 13-22
469	4-n-butylaniline	rat	149	9.51	3.1	1	1	0.23	-0.64	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100: 1-7
470	butyl salicylate	rat	194.23	11.45	4.08	2	1	0.00002	-4.7	dimethyl isosorbide & 2-propanol	full-thickness	not available	static	isotonic phosphate buffer	32 (skin)	48	HPLC	*Eur.J.Pharm.Sci*, 17: 95-104
471	caffeine	rat	194.2	32.83	0.16	4	0	0.00031	-3.51	petrolatum	full-thickness	back	static	saline & thimerosol	32	not available	radiolabelled (14C)	*Toxicol.Appl.Pharmacol*, 62: 474-480
472	caffeine	rat	194.2	32.83	0.16	4	0	0.001025	-2.99	50% aq. ethanol	full-thickness	not available	flow-through	saline	37	24	radiolabelled (14C)	*Toxicology*, 178: 65-66
473	clebopride	rat	373.9	11.47	3.21	4	2	0.0074	-2.13	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci*, 83: 29-32
474	clotrimazole	rat	344.85	11.17	6.26	2	0	0.0055	-2.26	propylene glycol	full-thickness	unknown	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215: 51-56
475	cortisone	rat	360.5	12.10	1.81	5	2	0.00017	-3.77	water	full-thickness skin	back	static	saline & thimerosal	32	not available	radiolabelled (3H)	*J.Soc.Cosmet.Chem*, 34: 127-135

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
476	cortisone	rat	360.5	12.10	1.81	5	2	0.00122	-2.91	water	full-thickness skin	abdomen	static	saline & thimerosal	32	not available	radiolabelled (3H)	*J.Soc.Cosmet.Chem*, 34: 127-135
477	cortisone	rat	360.5	12.10	1.81	5	2	0.00047	-3.33	water	full-thickness skin	abdomen	static	saline & thimerosal	32	not available	radiolabelled (3H)	*J.Soc.Cosmet.Chem*, 34: 127-135
478	coumarin	rat	146.15	11.91	1.51	1	0	0.00076	-3.12	ethanol	full-thickness skin	dorsal	flow-through	HEPES buffered HBSS & 0.5% gentamycin	32(skin)	72	radiolabelled	*Toxicol.Appl.Pharmacol*, 145: 34-42
479	coumarin	rat	146.15	11.91	1.51	1	0	0.00079	-3.1	ethanol	full-thickness skin	dorsal	flow-through	HEPES buffered HBSS & 0.5% gentamycin	32(skin)	72	radiolabelled	*Toxicol.Appl.Pharmacol*, 145: 34-42
480	o-cresyl glycidyl ether (oCGE)	rat	164.2	10.38	2.16	2	0	0.000134	-3.87	acetone	dermatomed skin	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
481	decane	rat	142.3	7.58	5.25	0	0	9.3 E-05	-4.03	JP-8	dermatomed 0.56 mm	back	static	6% Volpo 20 in PBS		4	GC	*Toxicol.Sci*., 55: 247-255
482	DDT	rat	354.49	9.45	6.79	0	0	0.0068	-2.17	acetone	dermatomed 0.5mm	back	flow-through	Hanks HEPES buffered medium, 4% BSA & gentamycin	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 1225-1232
483	DEHP	rat	390.57	9.39	8.39	2	0	0.000946	-3.02	acetone	isol. epidermis	back	flow-through	50% aq. ethanol	31.5 (skin)	72	radiolabelled (14C)	*Toxicol.Vitro*, 12: 47-55
484	DEHP	rat	390.57	9.39	8.39	2	0	0.0000983	-4.01	acetone	isol. dermis	back	flow-through	50% aq. ethanol	31.5 (skin)	72	radiolabelled (14C)	*Toxicol.Vitro*, 12: 47-55
485	DEHP	rat	390.57	9.39	8.39	2	0	0.000013	-4.89	acetone	isol. epidermis	back	flow-through	PBS	31.5 (skin)	72	radiolabelled (14C)	*Toxicol.Vitro*, 12: 47-55
486	DEHP	rat	390.57	9.39	8.39	2	0	0.0000476	-4.32	acetone	isol. dermis	back	flow-through	PBS	31.5 (skin)	72	radiolabelled (14C)	*Toxicol.Vitro*, 12: 47-55
487	DEP	rat	222.24	10.51	2.65	2	0	0.00037	-3.43	none	isol. epidermis	abdomen	static	50% aq. ethanol	30 (not available)	8	radiolabelled (14C)	*Environ.Health Perspect*., 74: 223-227
488	dibutylphthalate	rat	278.35	10.86	5.11	2	0	0.000037	-4.43	none	full-thickness skin	dorsal	static	RPMI & 2% bovine albumin & 1% antibiotics	36	24	radiolabelled (14C)	*Drug Met.Disp*., 29: 843-853
489	dibutylphthalate	rat	278.35	10.86	5.11	2	0	0.000089	-4.05	none	isol. epidermis	abdomen	static	50% aq. ethanol	30 (not available)	8	radiolabelled (14C)	*Environ.Health Perspect*., 74: 223-227
490	diethylene glycol monomethyl ether	rat	120.2	10.25	-1.5	3	1	0.08	-1.09	JP-8	dermatomed 0.56 mm	back	static	6% Volpo 20 in PBS	32 (skin)	4	GC	*Toxicol*., 55: 247-255
491	2,4 dimethylamine	rat	266.13	9.52	0.84	3	2	0.00031	-3.51	comercial formulation Wilbur-Elis	dermatomed 0.3 mm	back	flow-through	HBSS, HEPES buffer BSA & gentamycin sulphate	37	not available	radiolabelled (14C)	*Toxicol.Vitro*, 11: 251-262
492	dinoseb	rat	240.22	11.10	3.67	2	1	0.0008625	-3.06	acetone	dermatomed 0.35	dorsal	static	MEM, 4% FBS, aspartic acid, serine & gentamycin	32	not available	radiolabelled (14C)	*Fundam.Appl.Toxicol*., 19: 258-267
493	dinoseb	rat	240.22	11.10	3.67	2	1	0.00115	-2.94	acetone	dermatomed 0.35	dorsal	static	MEM, 4% FBS, aspartic acid, serine & gentamycin	32	not available	radiolabelled (14C)	*Fundam.Appl.Toxicol*., 19: 258-267
494	dodecane	rat	170.34	7.69	6.23	0	0	0.000014	-4.85	JP-8	dermatomed 0.56 mm	back	static	6% Volpo 20 in PBS	32 (skin)	4	GC	*Toxicol*., 55: 247-255
495	dodecyl decaethoxylate	rat	482.9	not calc.	4.33	not calc.	not cal.	0.000429	-3.37	methanol	dermatomed 0.24 mm	dorsal	static	aq. ethanol	37	24	radiolabelled (14C)	*Toxicol. Vitro*, 12: 57-65
496	dodecyl decaethoxylate	rat	482.9	not calc.	4.33	not calc.	not calc.	0.0000049	-5.31	methanol	dermatomed 0.24 mm	dorsal	flow-through	MEM & penicillin & streptomycin	37	24	radiolabelled (14C)	*Toxicol. Vitro*, 12: 57-65
497	dodecyl decaethoxylate	rat	482.9	not calc.	4.33	not calc.	not calc.	0.000429	-3.37	methanol	dermatomed 0.28 mm	dorsal	static	50% aq. ethanol	35	24	radiolabelled (14C)	*Arch. Toxicol*., 69: 649-654
498	dodecyl glycidyl ether (C12GE)	rat	242.2	8.41	5.01	2	0	0.000029	-4.54	acetone	dermatomed skin	dorsal	flow-through	HEPES, HBSS & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
499	dodecyl monoethoxylate	rat	230.4	9.16	4.5	2	1	0.00546	-2.26	methanol	dermatomed 0.24 mm	dorsal	static	aq. ethanol	37	24	radiolabelled (14C)	*Toxicol. Vitro*, 12: 57-65
500	dodecyl monoethoxylate	rat	230.4	9.16	4.5	2	1	0.00000032	-6.49	methanol	dermatomed 0.24 mm	dorsal	flow-through	MEM & penicillin & streptomycin	37	24	radiolabelled (14C)	*Toxicol. Vitro*, 12: 57-65
501	domperidone	rat	425.92	12.48	3.35	3	2	0.0028	-2.55	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci*, 83: 29-32
502	epikote YX4000	rat	354.4	11.00	5.19	4	0	0.098	-1.01	acetone	dermatomed skin	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
503	erioglaucine	rat	793.86	not calc.	-1.5	not calc.	not calc.	0.00000396	-5.4	40% propylene glycol	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol*., 42: 468-472

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
504	erioglaucine	rat	793.86	not calc.	-1.5	not calc.	not calc.	0.00001322	-4.88	propylene glycol & dodecylazacyclohe-ptan-2-one	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42: 468-472
505	erioglaucine	rat	793.86	not calc.	-1.5	not calc.	not calc.	0.00000542	-5.27	40% propylene glycol & 5% dimethylsulphoxide	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42: 468-472
506	erioglaucine	rat	793.86	not calc.	-1.5	not calc.	not calc.	0.000075	-4.12	40% propylene glycol & 2.25% sodium lauryl sulphate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42: 468-472
507	erioglaucine	rat	793.86	not calc.	-1.5	not calc.	not calc.	0.0000099	-5.00	40% propylene glycol & 1% dodecyl-L-pyroglutamate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42: 468-472
508	erioglaucine	rat	793.86	not calc.	-1.5	not calc.	not calc.	0.00002	-4.70	40% propylene glycol & 10% N-Methyl-2-pyrrolidone	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42: 468-472
509	erioglaucine	rat	793.86	not calc.	-1.5	not calc.	not calc.	0.0000197	-4.70	40% propylene glycol & 12% N-Methyl-2-pyrrolidone	full-thickness	abdomen	static	saline	37	26	spectrophotometry	*J.Pharm.Pharmacol.*, 42: 468-472
510	ethanol	rat	46.07	10.92	-0.14	1	1	0.000415	-3.38	water	full-thickness	back	static	saline	30	6	radiolabelled (14C)	*J.Invest.Dermatol*, 96: 921-925
511	ethylaniline	rat	121.2	9.73	2.11	1	1	0.115	-0.94	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100: 1-7
512	ethyl benzene	rat	106.2	9.04	3.03	0	0	0.00031	-3.51	JP-8	dermat. 0.56 mm	back	static	6% Volpo 20 in PBS	32 (skin)	4	GC	*Toxicol. Sci*, 55: 247-255
513	2-ethoxyethanol	rat	90.12	10.33	-0.42	2	1	0.000078	-4.11	methanol	dermat. 0.33 mm	dorsal	flow-through	MEM sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl. Pharmacol.*, 180: 74-82
514	2-ethoxyethanol	rat	90.12	10.33	-0.42	2	1	0.00023	-3.64	methanol	full-thickness	dorsal	flow-through	MEM sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl. Pharmacol.*, 180: 74-82
515	2-ethoxyethanol	rat	90.12	10.33	-0.42	2	1	0.000148	-3.83	none	dermat. 0.33 mm	dorsal	flow-through	MEM sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl. Pharmacol.*, 180: 74-82
516	2-ethoxyethanol	rat	90.12	10.33	-0.42	2	1	0.000075	-4.12	none	full-thickness	dorsal	flow-through	MEM sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl. Pharmacol.*, 180: 74-82
517	felodipine	rat	384.3	10.43	3.86	3	1	0.004	-2.40	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci*, 80: 931-934
518	fenoxapropethyl	rat	361.78	11.06	4.95	5	0	0.00071	-3.15	acetone	dermatom. 0.6 mm	back	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol. Vitro*, 6: 53-59
519	fenoxapropethyl	rat	361.78	11.06	4.95	5	0	0.00035	-3.46	acetone	dermatom. 0.9 mm	back	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol. Vitro*, 6: 53-59
520	fenoxapropethyl	rat	361.78	11.06	4.95	5	0	0.00035	-3.46	acetone	dermatom. 0.8 mm	back	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol. Vitro*, 6: 53-59
521	haloperidol	rat	375.9	10.78	4.22	4	1	0.02	-1.70	lactic acid & antibacterial antimycotic solution	full-thickness	abdomen	flow-through	0.03% v/v lactic acid solution	37	48	RP HPLC	*Int.J.Pharm*, 212: 247-255
522	1,6-hexanediol diglycidyl ether (HDDGE)	rat	230.2	9.36	0.84	4	0	0.000402	-3.40	acetone	dermatomed	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
523	4-n-hexylaniline	rat	177.3	9.68	4.08	1	1	0.229	-0.64	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100: 1-7
524	hydroquinone	rat	110.11	15.18	1.03	2	2	2.26 E-05	-4.66	not available	full-thickness	abdomen	static	Dulbecco's PBS, antibiotics and fungicides	30	8	radiolabelled (14C)	*Toxicol.Lett.*, 80: 167-172
525	ketoprofen	rat	254.29	11.75	3.12	2	1	0.0187	-1.73	IPM	full-thickness	not available	static	ethanol	32	8	HPLC	*Int.J.Pharm*, 262: 13-22
526	linoleic acid	rat	289.45	9.05	7.51	1	1	0.000029	-4.54	ethanol	full-thickness	sides, abdomen and back	static	phosphate Bbffer & pluronic F68 & BHT	37	95	radiolabelled (14C)	*J.Pharm.Pharmacol.*, 34: 610-611
527	lorazepam	rat	321.16	12.91	2.41	3	2	0.000051	-4.29	50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm*, 250: 359-369
528	lorazepam	rat	321.16	12.91	2.41	3	2	0.0001146	-3.94	0.5% Tween 80 & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm*, 250: 359-369
529	lorazepam	rat	321.16	12.91	2.41	3	2	0.000078	-4.11	5% Tween 80 & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm*, 250: 359-369

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
530	lorazepam	rat	321.16	12.91	2.41	3	2	0.0001994	-3.70	0.5% benzalkonium Cl & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm*, 250: 359-369
531	lorazepam	rat	321.16	12.91	2.41	3	2	0.0003591	-3.44	5% benzalkonium Cl & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm*, 250: 359-369
532	lorazepam	rat	321.16	12.91	2.41	3	2	0.0001501	-3.82	0.5% SLS & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm*, 250: 359-369
533	lorazepam	rat	321.16	12.91	2.41	3	2	0.0005662	-3.25	5% SLS & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm*, 250: 359-369
534	mannitol	rat	182.17	18.53	-3.01	6	6	0.000323	-3.49	dist. water	full-thickness	dorsal	static	0.9% physiological saline	30	96	radiolabelled (14C)	*Pharm.Res*, 9: 884-887
535	mannitol	rat	182.17	18.53	-3.01	6	6	0.00023	-3.64	dist. water	isol.epidermis	dorsal	static	0.9% physiological saline	30	96	radiolabelled (14C)	*Pharm.Res*, 9: 884-887
536	mannitol	rat	182.17	18.53	-3.01	6	6	0.000579	-3.24	dist. water	full-thickness	dorsal	static	0.9% physiological saline	not available	not available	radiolabelled (14C)	*Toxicol.Vitro*, 8: 827-830
537	mannitol	rat	182.17	18.53	-3.01	6	6	0.00087	-3.06	dist. water	isol. epidermis	dorsal	static	0.9% physiological saline	not available	not available	radiolabelled (14C)	*Toxicol.Vitro*, 8: 827-830
538	mannitol	rat	182.17	18.53	-3.01	6	6	0.000905	-3.04	dist. water	isol. epidermis	dorsal		0.9% physiological saline	32	not available	radiolabelled (14C)	*Toxicol.Vitro*, 8: 827-830
539	mannitol	rat	182.17	18.63	-3.01	6	6	0.000399	-3.40	dist. water	dermat. 0.23 mm	dorsal	static	0.9% physiological saline	not available	not available	radiolabelled (14C)	*Toxicol.Vitro*, 8: 827-830
540	mannitol	rat	182.17	18.63	-3.01	6	6	0.000872	-3.06	dist. water	dermat. 0.23 mm	dorsal	flow-through	0.9% physiological saline	32	not available	radiolabelled (14C)	*Toxicol.Vitro*, 8: 827-830
541	mannitol	rat	182.17	18.63	-3.01	6	6	0.00134	-2.87	water	full-thickness	back	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol.*, 96: 921-925
542	mefenamic acid	rat	241.29	11.85	5.28	2	0	0.0077	-2.11	IPM	full-thickness	not available	static	ethanol	32	8	HPLC	*Int.J.Pharm*, 262: 13-22
543	4-methylaniline	rat	107.2	10.58	1.62	1	1	0.08549	-1.07	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100: 1-7
544	methyl nicotinate	rat	137.14	11.80	0.64	2	0	0.00325	-2.49	Transcutol	full-thickness skin	abdomen	static	0.9~% sodium chloride	30 (skin)	not available	HPLC	*J.Pharm.Sci*, 80: 54-56
545	methyl nicotinate	rat	137.14	11.80	0.64	2	0	0.00278	-2.56	Transcutol, Labrafac Hydrophile & DPPG	full-thickness skin	abdomen	static	0.9~% sodium chloride	30 (skin)	not available	HPLC	*J.Pharm.Sci*, 80: 54-56
546	methyl nicotinate	rat	137.14	11.80	0.64	2	0	0.00222	-2.65	Labrafac Hydrophile	full-thickness skin	abdomen	static	0.9~% sodium chloride	30 (skin)	not available	HPLC	*J.Pharm.Sci*, 80: 54-56
547	methyl nicotinate	rat	137.14	11.80	0.64	2	0	0.00663	-2.18	Propylene glycol dipelargonate	full-thickness skin	abdomen	static	0.9~% sodium chloride	30 (skin)	not available	HPLC	*J.Pharm.Sci*, 80: 54-56
548	2-(2-ethoxyethoxy) ethanol	rat	120.15	10.25	-1.18	3	1	0.08	-1.10	JP-8	dermat. 0.56 mm	back	static	6% Volpo 20 in PBS	32 (skin)	4	GC	*Toxicol.Sci.*,55: 247-255
549	metochloropramide	rat	354.3	11.13	1.69	4	2	0.0091	-2.04	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci*, 83: 29-32
550	metopimazine	rat	445.61	13.55	2.42	3	1	0.0051	-2.29	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci*, 83: 29-32
551	N-N-diethyl m-toluamide	rat	191.28	10.70	2.26	1	0	0.00168	-2.77	acetone	dermat.0.5mm	back	flow-through	sterile Ringer's solution, Trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 7: 141-148
552	naphthalene	rat	128.2	10.42	3.17	0	0	0.00051	-3.29	JP-8	dermat.0.56mm	back	static	6% Volpo 20 in PBS	32 (skin)	4	GC	*Toxicol.Sci.*, 55: 247-255
553	nicardipine	rat	479.54	10.87	3.9	5	1	0.0049	-2.31	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci*, 80: 931-934
554	nicorandil	rat	211.18	14.40	0.43	3	1	0.000727	-3.14	water	full-thickness	abdomen	static	saline	37	32	HPLC	*J.Pharm.Pharmacol.*, 41: 379-383
555	nifedipine	rat	346.3	10.92	4.04	4	0	0.0017	-2.77	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci*, 80: 931-934
556	nimodipine	rat	418.4	10.50	3.13	3	1	0.0026	-2.59	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci*, 80: 931-934

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
557	nitrendipine	rat	360.4	11.44	2.99	5	1	0.0039	-2.41	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci*, 80: 931-934
558	nonane	rat	128.3	7.51	4.76	0	0	0.000042	-4.38	JP-8	dermatom. 0.56 mm	back	static	6% Volpo in PBS	32 (skin)	4	GC	*Toxicol.Sci.*, 55: 247-255
559	paraquat	rat	257.16	10.45	-2.71	0	0	0.000346	-3.46	water	full-thickness	back	static	saline	30	6	radiolabelled (14C)	*J.Invest.Dermatol.*, 96: 921-925
560	4-n-pentylaniline	rat	163.3	9.79	3.59	1	1	0.248	-0.61	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100: 1-7
561	2-phenoxyethanol	rat	138.17	11.49	1.1	2	1	0.00272	-2.57	methanol	dermatom. 0.24 mm	dorsal	static	50% aq. ethanol	37	24	radiolabelled (14C)	*Food Chem.Toxicol*, 35: 1009-1016
562	2-phenoxyethanol	rat	138.17	11.49	1.1	2	1	2.72E -05	-4.57	methanol	dermatom. 0.24 mm	dorsal	static	aq. ethanol	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12: 57-65
563	2-phenoxyethanol	rat	138.17	11.49	1.1	2	1	1.76E-05	-4.75	methanol	dermatom. 0.24 mm	dorsal	flow-through	MEM & penicillin / streptomycin+CO2	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12: 57-65
564	2-phenoxyethanol	rat	138.17	11.49	1.1	2	1	0.001764	-2.75	methanol	dermatom. 0.24 mm	dorsal	flow-through	MEM & penicillin / streptomycin+CO2	37	24	radiolabelled (14C)	*Food Chem.Toxicol*, 35: 1009-1016
565	2-phenoxyethanol	rat	138.17	11.49	1.1	2	1	0.00735	-2.13	methanol	dermatom. 0.24 mm	dorsal	static	50% aq. ethanol	37	24	radiolabelled (14C)	*Food Chem.Toxicol*, 35: 1009-1016
566	2-phenylphenol	rat	170.21	12.24	3.28	1	1	0.00097	-3.01	60% aq. ethanol	full-thickness skin	dorsal / flank	static	MEM, 10% heat-inactivated BSA, 2mM l-glutamine & 0.05mg/ml gentamycine	32	48	radiolabelled (14C)	*Toxicol.Pharmacol.*, 35: 198-208
567	2-phenylphenol	rat	170.21	12.24	3.28	1	1	0.0266	-1.58	60% aq. ethanol	isolated epidermis	dorsal / flank	static	Saline (0.9% NaCl), 0.01% sodium azide & 3% BSA	32	48	radiolabelled (14C)	*Toxicol.Pharmacol.*, 35: 198-208
568	4-n-propylaniline	rat	135	10.10	2.61	1	1	0.169	-0.77	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100: 1-7
569	propoxur	rat	209.25	10.31	1.9	2	1	0.00052	-3.28	60% aq. ethanol	full-thickness	dorsal	static	culture medium 10% fetal bovine serum	32	24	radiolabelled (14C)	*Toxicol.Sci.*, 58: 15-22
570	propoxur	rat	209.25	10.31	1.9	2	1	0.00375	-2.43	60% aq. ethanol	isol. epidermis	dorsal	static	saline & sodium azide, BSA	32	24	radiolabelled (14C)	*Toxicol.Sci.*, 58: 15-22
571	salicylamide	rat	137.14	16.60	1.03	2	2	0.000017	-4.77	dimethyl isosoride & 2-propanol	full-thickness	not available	static	isotonic phosphate buffer	32 (skin)	48	HPLC	*Eur. J.Pharm.Sci.*, 17: 95-104
572	salicylic acid	rat	138.1	14.39	2.24	2	2	0.01046	-1.98	phosphate buffer (pH2)	full-thickness	dorsal	static	tris. HCL buffer sol.	25	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418
573	salicylic acid	rat	138.1	14.39	2.24	2	2	0.0073	-2.14	citric acid phosphate (pH3)	full-thickness	dorsal	static	tris. HCL buffer sol.	25	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418
574	salicylic acid	rat	138.1	14.39	2.24	2	2	0.00132	-2.88	citric acid phosphate (pH4)	full-thickness	dorsal	static	tris. HCL buffer sol.	25	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418
575	salicylic acid	rat	138.1	14.39	2.24	2	2	0.0248	-1.61	citric acid phosphate (pH2)	full-thickness	dorsal	static	tris. HCL buffer sol.	25	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418
576	salicylic acid	rat	138.1	14.39	2.24	2	2	0.000024	-4.62	dimethyl isosoride & 2-propanol	full-thickness	not available	static	isotonic phosphate buffer	32 (skin)	48	HPLC	*Eur. J.Pharm.Sci.*, 17: 95-104
577	scopolamine	rat	303.4	11.53	0.39	4	1	0.0041	-2.39	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci*, 83: 29-32
578	terbinafine	rat	291.4	9.33	5.81	1	0	0.055	-1.26	propylene glycol	full-thickness	unknown	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm*, 215: 51-56
579	testosterone	rat	288.4	10.66	3.27	2	1	0.0002	-3.70	ethanol	isol.epidermis	abdomen	static	culture medium & 10% BSA	32	22	radiolabelled (14C)	Van de Sandt 2000
580	testosterone	rat	288.4	10.66	3.27	2	1	0.0018	-2.74	20% aq. ethanol	full-thickness	dorsal	static	saline & 40% polyethylene glycol	37 (not available)	24	HPLC & UV detector	*J.Pharm.Pharmacol.*, 52: 369-375
581	testosterone	rat	288.4	10.66	3.27	2	1	0.00013	-3.89	40% aq. ethanol	full-thickness	dorsal	static	saline & 40% polyethylene glycol	37 (not available)	24	HPLC & UV detector	*J.Pharm.Pharmacol.*, 52: 369-375
582	testosterone	rat	288.4	10.66	3.27	2	1	0.00007	-4.15	50% aq. ethanol	full-thickness	dorsal	static	saline & 40% polyethylene glycol	37 (not available)	24	HPLC & UV detector	*J.Pharm.Pharmacol.*, 52: 369-375
583	testosterone	rat	288.4	10.66	3.27	2	1	0.00002	-4.70	80% aq. ethanol	full-thickness	dorsal	static	saline & 40% polyethylene glycol	37 (not available)	24	HPLC & UV detector	*J.Pharm.Pharmacol.*, 52: 369-375
584	theophylline	rat	180.17	14.05	-0.39	4	1	0.00923	-2.03	1-propanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*, 40: 231-242

No	Name	Membrane	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) Water bath	Study duration (h)	Analytical technique	Reference
585	theophylline	rat	180.17	14.05	-0.39	4	1	0.0109	-1.96	ethanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*, 40: 231-242
586	theophylline	rat	180.17	14.05	-0.39	4	1	0.0139	-1.86	methanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*, 40: 231-242
587	theophylline	rat	180.17	14.05	-0.39	4	1	0.0022	-2.66	water	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*, 40: 231-242
588	toluene (methyl benzene)	rat	92.1	9.14	2.54	0	0	0.0011	-2.96	JP-8	dermatom. 0.56 mm	back	static	6% Volpo 20 in PBS	32 (skin)	4	GC	*Toxicol. Sci.*, 55: 247-255
589	triclosan	rat	289.55	10.02	2.47	2	1	1.36	0.13	90% aq. ethanol	dermatomed 0.28 mm	dorsal	flow-through	Eagles MEM & Earles salts buffered to pH7.3	32	24	radiolabelled (14C)	*J.Pharmacol.Exp.Ther.*, 38: 361-370
590	tridecane	rat	185.4	7.74	6.73	0	0	0.000015	-4.82	JP-8	dermatomed 0.56 mm	back	static	6% Volpo 20 in PBS	32 (skin)	4	GC	*Toxicol. Sci.*, 55: 247-255
591	undecane	rat	156.31	7.64	5.74	0	0	0.000025	-4.60	JP-8	dermatom. 0.56 mm	back	static	6% Volpo 20 in PBS	32 (skin)	4	GC	*Toxicol. Sci.*, 55: 247-255
592	xylene (dimethyl benzene)	rat	106.2	9.10	3.09	0	0	0.00017	-3.77	JP-8	dermatom. 0.56 mm	back	static	6% Volpo 20 in PBS	32 (skin)	4	GC	*Toxicol. Sci.*, 55: 247-255
593	water	rat	18.02	26.68	-1.38	1	1	0.00738	-2.13	0.9% saline	isol. epidermis	back	flow-through	50% aq. ethanol	31.5 (skin)	5	radiolabelled (3H)	*Toxicol. Vitro*, 12: 47-55
594	water	rat	18.02	26.68	-1.38	1	1	0.00175	-2.77	0.9% saline	isol. epidermis	back	flow-through	PBS	31.5 (skin)	5	radiolabelled (3H)	*Toxicol. Vitro*, 12: 47-55
595	water	rat	18.02	26.68	-1.38	1	1	0.0517	-1.29	0.9% saline	isol. dermis	back	flow-through	PBS	31.5 (skin)	5	radiolabelled (3H)	*Toxicol. Vitro*, 12: 47-55
596	water	rat	18.02	26.68	-1.38	1	1	0.00143	-2.84	0.9% physiological saline	full-thickness	dorsal	static	0.9 % physiological saline	30	96	radiolabelled (14C)	*Pharmaceut.Res.*, 9: 884-887
597	water	rat	18.02	26.68	-1.38	1	1	0.00116	-2.94	0.9% physiological saline	isol. epidermis	dorsal	static	0.9 % physiological saline	30	96	radiolabelled (14C)	*Pharmaceut.Res.*, 9: 884-887
598	water	rat	18.02	26.68	-1.38	1	1	0.00194	-2.71	saline	full-thickness	dorsal	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol. Vitro*, 8: 827-830
599	water	rat	18.02	26.68	-1.38	1	1	0.0014	-2.85	saline	isol. epidermis	dorsal	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol. Vitro*, 8: 827-830
600	water	rat	18.02	26.68	-1.38	1	1	0.00198	-2.7	dist. water	dermatomed 0.23 mm	dorsal	flow-through	0.9% physiological saline	32	not available	radiolabelled (3H)	*Toxicol. Vitro*, 8: 827-830

Appendix 4. Lipophilicity

Set 1. Human skin data

Subgroup 1		Subgroup 2		Subgroups 3 and 4	
Name	Log P KOWWIN	Name	Log P KOWWIN	Name	Log P KOWWIN
glyphosate	-4.47	nicotine	1.00	etorphine	3.02
mannitol	-3.01	hydroquinone	1.03	meperidine	3.03
paraquat	-2.71	resorcinol	1.03	4-n-butylaniline	3.10
erioglaucine	-1.50	aniline	1.08	naproxene	3.10
water	-1.38	2-phenoxyethanol	1.10	n-hexyl nicotinate	3.10
doxycycline HCL	-1.36	ethyl nicotinate	1.13	ketoprofen	3.12
methotrexate	-1.28	codeine	1.28	cortexolone	3.15
n-nitrosodiethanolamine	-1.28	naltrexone (NTX)	1.39	chloroxylenol	3.25
2-(2-methoxyethoxy)ethanol	-1.18	pirimicarb	1.40	testosterone	3.27
adenosine	-1.05	prednisone	1.46	2-phenylphenol	3.28
dimethylformamide	-0.93	NTX-3-acetate (ACE-NTX)	1.47	estrone	3.43
2-methoxyethanol	-0.91	prednisolone	1.49	butyl paraben	3.47
methanol	-0.84	coumarin	1.51	thymol	3.52
5-fluorouracil	-0.81	phenol	1.51	4-n-pentylaniline	3.59
2-(2-ethoxyethoxy)ethanol	-0.69	2-phenylethanol	1.57	sufentanil	3.62
nikel	-0.57	hydromorphone	1.60	progesterone	3.67
deoxyadenosine	-0.55	hydrocortisone	1.61	parathion	3.73
1-methoxylpropan-2-ol	-0.49	ITF 296	1.61	ibuprofen	3.79
squaric acid	-0.44	aldosterone	1.63	bisphenol A diglycidyl ether (BADGE)	3.84
nizatidine	-0.43	lidocaine	1.66	diazinon	3.86
2-ethoxyethanol	-0.42	metoprolol	1.69	fentanyl	3.89
theophylline	-0.39	cortisone	1.81	pregnenolone	3.89
boric acid	-0.22	oxprenolol	1.83	NTX-3 heptanoate (HEP-NTX)	3.92
ethanol	-0.14	bisoprolol	1.84	etodolac	3.93
atenolol	-0.03	benzoic acid	1.87	b-estradiol	3.94
caffeine	0.16	propoxur	1.90	ethinyl estradiol	4.00
2-(2-butoxyethoxy)ethanol	0.29	3-nitrophenol	1.91	dichlofenac	4.02
ranitidine	0.29	griseofulvin	1.92	diethyl squarate	4.07
cimetidine	0.40	celiprolol	1.93	prochloraz	4.13
nicorandil	0.43	NTX-3-propionate (PROP-NTX)	1.96	lindane	4.26
2-butoxyethanol	0.57	benzene	1.99	chlorpyrifos	4.66
2-ethoxyethyl acetate	0.59	corticosterone	1.99	nonane	4.76
methyl nicotinate	0.64	methyl paraben	2.00	flufenamic acid	4.88
nicotinic acid	0.69	methyl-4-hydroxy benzoate	2.00	dodecyl glycidyl ether (C12GE)	5.01
morphine	0.72	betamethasone	2.02	dibutylphthalate	5.11
isosorbide dinitrate (ISDN)	0.76	2-cresol (o-cresol)	2.06	epikote YX4000	5.19
1,6-hexanediol diglycidyl ether (HDDGE)	0.84	3-cresol (m-cresol)	2.06	terbinafine	5.81
2,4 dimethylamine	0.84	4-cresol (p-cresol)	2.06	clotrimazole	6.26
		butyl nicotinate	2.11	DDT	6.79
		ethylaniline	2.11	cannabinol	7.23
		o-cresyl glycidyl ether (oCGE)	2.16	linoleic acid	7.51
		nimesulide	2.22	Δ-tetrahydrocannabinol (THC)	7.60
		salicylic acid	2.24	cannabidiol	8.01
		N-N-diethyl m-toluamide	2.26	DEHP	8.39

Subgroup 1		Subgroup 2		Subgroups 3 and 4	
Name	Log P KOWWIN	Name	Log P KOWWIN	Name	Log P KOWWIN
		malathion	2.29	borax	28
		benzyl nicotinate	2.35		
		4-bromophenol	2.40		
		dibutyl squarate	2.45		
		NTX-3-butyrate (BUT-NTX)	2.45		
		NTX-3-valerate (VAL-NTX)	2.45		
		triclosan	2.47		
		4-phenylbutanol	2.55		
		propranolol	2.60		
		3,4 xylenol	2.61		
		DEP	2.65		
		2-naphthol	2.69		
		androstedione	2.75		
		methyl parathion	2.75		
		estriol	2.81		
		n-octanol	2.81		
		methiocarb	2.87		
		NTX-3-hexanoate (HEX-NTX)	2.94		

Set 2. Rat skin data

Subgroup 1		Subgroup 2		Subgroup 3	
Name	Log P KOWWIN	Name	Log P KOWWIN	Name	Log P KOWWIN
mannitol	-3.01	hydroquinone	1.03	ethyl benzene	3.03
paraquat	-2.71	salicylamide	1.03	xylene (dimethyl benzene)	3.09
diethylene glycol monomethyl ether	-1.50	aniline	1.08	4-n-butylaniline	3.10
erioglaucine	-1.50	2-phenoxyethanol	1.10	ketoprofen	3.12
water	-1.38	coumarin	1.51	nimodipine	3.13
2-(2-methoxyethoxy)ethanol	-1.18	4-methylaniline	1.62	naphthalene	3.17
2-ethoxyethanol	-0.42	metochloropramide	1.69	clebopride	3.21
theophylline	-0.39	alizapride	1.80	testosterone	3.27
ethanol	-0.14	cortisone	1.81	2-phenylphenol	3.28
caffeine	0.16	benzoic acid	1.87	domperidone	3.35
scopolamine	0.39	propoxur	1.90	4-n-pentylaniline	3.59
nicorandil	0.43	bromopride	1.94	dinoseb	3.67
aminopyrene	0.60	bufexamac	1.98	bisphenol A diglycidyl ether (BADGE)	3.84
methyl nicotinate	0.64	benzyl acetate	2.08	felodipine	3.86
2,4 dimethylamine	0.84	ethylaniline	2.11	nicardipine	3.90
1,6-hexanediol diglycidyl ether (HDDGE)	0.84	o-cresyl glycidyl ether (oCGE)	2.16	nifedipine	4.04
		salicylic acid	2.24	butyl salicylate	4.08
		N-N-diethyl m-toluamide	2.26	4-n-hexylaniline	4.08
		lorazepam	2.41	haloperidol	4.22
		metopimazine	2.42	dodecyl decaethoxylate	4.33
		triclosan	2.47	dodecyl monoethoxylate	4.50
		toluene (methyl benzene)	2.54	nonane	4.76
		4-n-propylaniline	2.61	fenoxapropethyl	4.95
		DEP	2.65	dodecyl glycidyl ether (C12GE)	5.01

Subgroup 1		Subgroup 2		Subgroup 3	
Name	Log P KOWWIN	Name	Log P KOWWIN	Name	Log P KOWWIN
		nitrendipine	2.99	dibutylphthalate	5.11
				epikote YX4000	5.19
				decane	5.25
				mefenamic acid	5.28
				undecane	5.74
				terbinafine	5.81
				dodecane	6.23
				clotrimazole	6.26
				tridecane	6.73
				DDT	6.79
				linoleic acid	7.51
				DEHP	8.39

Set 3. Mouse skin data

Subgroup 1		Subgroup 2		Subgroup 3	
Name	Log P KOWWIN	Name	Log P KOWWIN	Name	Log P KOWWIN
sucrose	-4.27	coumarin	1.51	etorphine	3.02
urea	-1.56	hydrocortisone	1.62	17a-hydroxyprogesterone	3.08
erioglaucine	-1.50	lidocaine	1.66	deoxycortisone	3.12
water	-1.38	n-heptanol	1.82	alachlor	3.37
thiourea	-1.31	corticosterone	1.99	TDCPP	3.65
5-fluorouracil	-0.81	n-hexanol	2.03	progesterone	3.67
methanol	-0.63	o-cresyl glycidyl ether (oCGE)	2.16	bisphenol A diglycidyl ether (BADGE)	3.84
squaric acid	-0.44	salicylic acid	2.24	diethyl squarate	4.07
ethanol	-0.14	N-N-diethyl m-toluamide	2.26	prednisolone 21-heptanoate	4.60
atenolol	-0.03	dibutyl squarate	2.45	dodecyl glycidyl ether (C12GE)	5.01
caffeine	0.16	n-octanol	2.81	prednisolone 21-octanoate	5.09
nicorandil	0.43	atrazine	2.82	epikote YX4000	5.19
morphine	0.72			trifluralin	5.31
propranolol HCL	0.74			prednisolone 21-undecanoate	5.54
n-butanol	0.84			prednisolone 21-nonanoate	5.58
1,6-hexanediol diglycidyl ether (HDDGE)	0.84			prednisolone 21-tridecanoate	6.02
				prednisolone 21-decanoate	6.07
				prednisolone 21-pentadecanoate	6.79
				decabromodiphenyl oxide (DBDPO)	8.10
				etorphine	3.02

Set 4. Pig skin data

Subgroup 1		Subgroup 2	
Name	Log P KOWWIN	Name	Log P KOWWIN
mannitol	-3.01	2-phenylphenol	3.28
water	-1.38	ethyl ester	3.39
chlorogenic acid	-1.00	propyl ester	3.89
scopolamine	0.39	butyl ester	4.38
caprtopril	0.84	pentyl ester	4.87
ketoprofen	0.97	pentachlorophenol	5.12

Subgroup 1		Subgroup 2	
Name	Log P KOWWIN	Name	Log P KOWWIN
cafeic acid	1.10	hexyl ester	5.36
tropicamide	1.19	terbinafine	5.81
atropine	1.91		
ligustrazine hydrochloride	2.18		
salicylic acid	2.24		
methyl ester	2.90		

Set 5. Membrane data

Subgroup 1		Subgroup 2	
Name	Log P KOWWIN	Name	Log P KOWWIN
caffeine	0.16	amethocaine	3.02
captopril	0.84	testosterone	3.27
benzocaine	1.80	ethyl ester	3.39
benzoic acid	1.87	ketocaine	3.60
procaine	1.99	propyl ester	3.89
salicylic acid	2.24	dibucaine	4.04
methyl ester	2.90	butyl ester	4.38
		pentyl ester	4.87
		flufenamic acid	4.88
		pentachlorophenol	5.12
		hexyl ester	5.36
		terbinafine	5.81
		clotrimazole	6.26
		DDT	6.79

Appendix 5. Human skin dataset

Group A1

Type of skin: human | Site: abdominal | 32 °C at the surface of the skin | Time of 24-48 h | HPLC / GC / radiolabelled | Vehicle: water | propylene glycol | Receptor fluid | normal saline | HEPES-buffered Hanks´ balanced salt solution

Cell type: flow through cells | 37 °C in WB | physiological buffer | ethanol, methanol

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	caffeine	194.2	32.83	0.16	4	0	0.00021	-3.68	ethylene glycol	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol.*, 115: 1-11
2	caffeine	194.2	32.83	0.16	4	0	0.00051	-3.29	water gel	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol.*, 115: 1-12
3	cannabinol	310.46	10.9	7.23	2	1	0.00015	-3.82	propylene glycol : water (7:3) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol*., 56: 291-297
4	cannabidiol	314.46	11.11	8.01	2	2	0.00024	-3.62	propylene glycol : water (7:3) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol*., 56: 291-297
5	diazinon	304.35	14.98	3.86	2	1	0.0095	-2.02	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, trizma, glucose	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 1219-1224
6	DDT	354.49	9.45	6.79	0	0	0.00594	-2.23	acetone	dermatomed 0.5 mm	abdomen	flow-through	Hanks HEPES buffered medium, 4% BSA & gentamycin	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 1225-1232
7	mannitol	182.17	18.63	-3.01	6	6	0.000025	-4.60	dist. water	isol. epidermis	abdomen	flow-through	0.9% physiological saline	32	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 827-830
8	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00224	-2.65	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 7: 141-148
9	testosterone	288.4	10.66	3.27	2	1	0.00018	-3.74	ethylene glycol	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115: 1-11
10	testosterone	288.4	10.66	3.27	2	1	0.00671	-2.17	water gel	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115: 1-11
11	Δ-tetrahydrocannabinol (THC)	314.46	9.75	7.6	2	1	0.000028	-4.55	propylene glycol : water : ethanol (9:1:1) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol*., 56: 291-297
12	isosorbide dinitrate (ISDN)	236.14	10.36	0.76	4	0	0.00449	-2.35	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11: 59-68
13	nicorandil	211.18	14.40	0.43	3	1	0.00005	-4.30	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11: 59-68

Group A2

Type of skin: human | Site: abdominal | 32 °C at the surface of the skin | Time of 24-48 h | HPLC / GC / radiolabelled | Vehicle: water | propylene glycol | Receptor fluid | normal saline | HEPES-buffered Hanks´ balanced salt solution

Cell type: flow through cells | 37 °C in WB | physiological buffer | ethanol, methanol

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	caffeine	194.2	32.83	0.16	4	0	0.00021	-3.68	ethylene glycol	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol.*, 115: 1-11
2	caffeine	194.2	32.83	0.16	4	0	0.00051	-3.29	water gel	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol.*, 115:1-11
3	cannabinol	310.46	10.9	7.23	2	1	0.00015	-3.82	propylene glycol : water (7:3) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol*., 56: 291-297
4	cannabidiol	314.46	11.11	8.01	2	2	0.00024	-3.62	propylene glycol : water (7:3) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol*., 56: 291-297
5	diazinon	304.35	14.98	3.86	2	1	0.0095	-2.02	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, trizma, glucose	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 1219-1224

No	Name	MW	SP (cal/cm^3)$^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
6	DDT	354.49	9.45	6.79	0	0	0.00594	-2.23	acetone	dermatomed 0.5 mm	abdomen	flow-through	Hanks HEPES buffered medium, 4% BSA & gentamycin	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 1225-1232
7	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00224	-2.65	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 7: 141-148
8	testosterone	288.4	10.66	3.27	2	1	0.012	-1.92	0.1M phosphate buffer pH1	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
9	testosterone	288.4	10.66	3.27	2	1	0.0117	-1.93	0.1M phosphate buffer pH2	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
10	testosterone	288.4	10.66	3.27	2	1	0.00912	-2.04	hydrochloric acid and potassium chloride pH2	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
11	testosterone	288.4	10.66	3.27	2	1	0.012	-1.92	0.1M phosphate buffer pH6	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
12	testosterone	288.4	10.66	3.27	2	1	0.04	-1.40	0.1M phosphate buffer pH12	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
13	testosterone	288.4	10.66	3.27	2	1	0.00018	-3.74	ethylene glycol	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115: 1-11
14	testosterone	288.4	10.66	3.27	2	1	0.00671	-2.17	water gel	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115: 1-11
15	Δ-tetrahydrocannabinol (THC)	314.46	9.75	7.6	2	1	0.000028	-4.55	propylene glycol : water : ethanol (9:1:1) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol.*, 56: 291-297
16	mannitol	182.17	18.63	-3.01	6	6	0.000025	-4.60	dist. water	isol. epidermis	abdomen	flow-through	0.9% physiological saline	32	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 827-830
17	isosorbide dinitrate (ISDN)	236.14	10.36	0.76	4	0	0.00449	-2.35	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11: 59-68
18	nicorandil	211.18	14.40	0.43	3	1	0.00005	-4.30	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11: 59-68

Group A3

Type of skin: human | Site: abdominal / breast | 32 °C at the surface of the skin | Time of 24-48 h | HPLC / GC / radiolabelled | Vehicle: water | propylene glycol | Receptor fluid | normal saline | HEPES-buffered Hanks´ balanced salt solution

Cell type: flow through cells | 37 °C in WB | physiological buffer | ethanol, methanol

No	Name	MW	SP (cal/cm^3)$^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	caffeine	194.2	32.83	0.16	4	0	0.00021	-3.68	ethylene glycol	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol.*, 115: 1-11
2	caffeine	194.2	32.83	0.16	4	0	0.00051	-3.29	water gel	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol.*, 115: 1-11
3	cannabinol	310.46	10.9	7.23	2	1	0.00015	-3.82	propylene glycol : water (7:3) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol.*, 56: 291-297
4	cannabidiol	314.46	11.11	8.01	2	2	0.00024	-3.62	propylene glycol : water (7:3) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol.*, 56: 291-297
5	diazinon	304.35	14.98	3.86	2	1	0.0095	-2.02	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, trizma, glucose	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 1219-1224
6	DDT	354.49	9.45	6.79	0	0	0.00594	-2.23	acetone	dermatomed 0.5 mm	abdomen	flow-through	Hanks HEPES buffered medium, 4% BSA & gentamycin	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 1225-1232
7	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00224	-2.65	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 7: 141-148
8	testosterone	288.4	10.66	3.27	2	1	0.012	-1.92	0.1M phosphate buffer pH1	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
9	testosterone	288.4	10.66	3.27	2	1	0.0117	-1.93	0.1M phosphate buffer pH2	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
10	testosterone	288.4	10.66	3.27	2	1	0.00912	-2.04	hydrochloric acid and potassium chloride pH2	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
11	testosterone	288.4	10.66	3.27	2	1	0.012	-1.92	0.1M phosphate buffer pH6	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
12	testosterone	288.4	10.66	3.27	2	1	0.04	-1.40	0.1M phosphate buffer pH12	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
13	testosterone	288.4	10.66	3.27	2	1	0.00018	-3.74	ethylene glycol	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115: 1-11
14	testosterone	288.4	10.66	3.27	2	1	0.00671	-2.17	water gel	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115: 1-11
15	Δ-tetrahydrocannabinol (THC)	314.46	9.75	7.6	2	1	0.000028	-4.55	propylene glycol : water : ethanol (9:1:1) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol.*, 56: 291-297
16	isosorbide dinitrate (ISDN)	236.14	10.36	0.76	4	0	0.00449	-2.35	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11: 59-68
17	nicorandil	211.18	14.40	0.43	3	1	0.00005	-4.30	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11: 59-68
18	bisphenol A diglycidyl ether (BADGE)	340.8	10.38	3.84	4	0	4.80E-07	-6.32	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, BSA & gentamycin	32(skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
19	chlorpyrifos	350.59	10.10	4.66	1	0	0.00011	-3.96	ethanol	full-thickness	breast	flow-through	50% aq. ethanol	32 (skin)	24	gas chromatography	*Hum.Exp.Toxicol*, 19: 104-107
20	o-cresyl glycidyl ether (oCGE)	164.2	10.38	2.16	2	0	9.30E-05	-4.03	acetone	dermatommed	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
21	dodecyl glycidyl ether (C12GE)	242.2	8.41	5.01	2	0	0.00000331	-5.48	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
22	epikote YX4000	354.4	11.00	5.19	4	0	0.000000047	-7.33	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
23	1,6-hexanediol diglycidyl ether (HDDGE)	230.2	9.36	0.84	4	0	0.000136	-3.87	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32(skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
24	methiocarb	225.31	10.92	2.87	1	1	0.0011	-2.96	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*, 48: 697-701
25	pirimicarb	238.29	11.05	1.4	4	0	0.0027	-2.57	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*, 48: 697-701
26	prochloraz	376.7	10.69	4.13	3	0	0.0007	-3.15	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*, 48: 697-701
27	mannitol	182.17	18.63	-3.01	6	6	0.000025	-4.60	dist. water	isol. epidermis	abdomen	flow-through	0.9% physiological saline	32	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 827-830

Group A4

Type of skin: human | Site: all types | 32 °C at the surface of the skin | Time of 24-72 h | HPLC / GC / radiolabelled | Vehicle: water | propylene glycol | Receptor fluid | normal saline | HEPES-buffered Hanks´ balanced salt solution

Cell type: flow through cells | 37 °C in WB | physiological buffer | ethanol, methanol

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	caffeine	194.2	32.83	0.16	4	0	0.00021	-3.68	ethylene glycol	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol.*, 115: 1-11
2	caffeine	194.2	32.83	0.16	4	0	0.00051	-3.29	water gel	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol.*, 115: 1-11
3	cannabinol	310.46	10.9	7.23	2	1	0.00015	-3.82	propylene glycol : water (7:3) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol.*, 56: 291-297
4	cannabidiol	314.46	11.11	8.01	2	2	0.00024	-3.62	propylene glycol : water (7:3) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol.*, 56: 291-297
5	diazinon	304.35	14.98	3.86	2	1	0.0095	-2.02	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, trizma, glucose	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 1219-1224
6	DDT	354.49	9.45	6.79	0	0	0.00594	-2.23	acetone	dermatomed 0.5 mm	abdomen	flow-through	Hanks HEPES buffered medium, 4% BSA & gentamycin	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 1225-1232

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
7	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00224	-2.65	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 7: 141-148
8	testosterone	288.4	10.66	3.27	2	1	0.012	-1.92	0.1M phosphate buffer pH1	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
9	testosterone	288.4	10.66	3.27	2	1	0.0117	-1.93	0.1M phosphate buffer pH2	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
10	testosterone	288.4	10.66	3.27	2	1	0.00912	-2.04	hydrochloric acid and potassium chloride pH2	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
11	testosterone	288.4	10.66	3.27	2	1	0.012	-1.92	0.1M phosphate buffer pH6	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
12	testosterone	288.4	10.66	3.27	2	1	0.04	-1.40	0.1M phosphate buffer pH12	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
13	testosterone	288.4	10.66	3.27	2	1	0.00018	-3.74	ethylene glycol	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115: 1-11
14	testosterone	288.4	10.66	3.27	2	1	0.00671	-2.17	water gel	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115: 1-11
15	Δ-tetrahydrocannabinol (THC)	314.46	9.75	7.6	2	1	0.000028	-4.55	propylene glycol : water : ethanol (9:1:1) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol.*, 56: 291-297
16	isosorbide dinitrate (ISDN)	236.14	10.36	0.76	4	0	0.00449	-2.35	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11: 59-68
17	nicorandil	211.18	14.40	0.43	3	1	0.00005	-4.30	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11: 59-68
18	bisphenol A diglycidyl ether (BADGE)	340.8	10.38	3.84	4	0	4.80E-07	-6.32	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, BSA & gentamycin	32(skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
19	chlorpyrifos	350.59	10.10	4.66	1	0	0.00011	-3.96	ethanol	full-thickness	breast	flow-through	50% aq. ethanol	32(skin)	24	gas chromatography	*Hum.Exp.Toxicol*,19: 104-107
20	o-cresyl glycidyl ether (oCGE)	164.2	10.38	2.16	2	0	9.30E-05	-4.03	acetone	dermatommed	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*,30: 469-483
21	dodecyl glycidyl ether (C12GE)	242.2	8.41	5.01	2	0	0.00000331	-5.48	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
22	epikote YX4000	354.4	11.00	5.19	4	0	0.000000047	-7.33	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
23	1,6-hexanediol diglycidyl ether (HDDGE)	230.2	9.36	0.84	4	0	0.000136	-3.87	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32(skin)	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
24	methiocarb	225.31	10.92	2.87	1	1	0.0011	-2.96	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*,48:697-701
25	pirimicarb	238.29	11.05	1.4	4	0	0.0027	-2.57	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*,48:697-701
26	prochloraz	376.7	10.69	4.13	3	0	0.0007	-3.15	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*,48:697-701
27	benzoic acid	122.1	11.94	1.87	1	1	0.00133	-2.88	deionised water	dermatomed 0.6 mm	not available	flow-through	PBS	37	48	radiolabelled (14C)	*J.Pharm.Sci.*, 85:249-252
28	boric acid	61.83	44.06	-0.22	3	3	0.00029	-3.54	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
29	boric acid	61.83	44.06	-0.22	3	3	0.0000014	-5.85	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
30	boric acid	61.83	44.06	-0.22	3	3	0.00012	-3.92	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
31	boric acid	61.83	44.06	-0.22	3	3	0.0005	-3.30	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
32	coumarin	146.15	11.91	1.51	1	0	0.000376	-3.42	ethanol	full-thickness	breast	flow-through	HEPES buffered HBSS & 0.5% gentamycin	32 (skin)	72	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.*, 145:34-42
33	coumarin	146.15	11.91	1.51	1	0	0.000719	-3.14	ethanol	full-thickness	breast	flow-through	HEPES buffered HBSS & 0.5% gentamycin	32 (skin)	72	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.*, 145:34-42
34	glyphosate	169.10	12.73	-4.47	3	4	0.000459	-3.34	water	dermatom. 1mm	not available	flow-through	PBS	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*, 34:731-735

No	Name	MW	SP (cal/cm^3)$^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
35	ITF 1129	252	not calc.	not calc.	not calc.	not calc.	0.01085	-1.96	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
36	ITF 296	238	12.91	1.61	3	0	0.00356	-2.45	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
37	malathion	330.36	10.61	2.29	2	0	0.203	-0.69	aq. ethanol	dermat. 1mm	not available	flow-through	PBS	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,34:731-735
38	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.000025	-4.60	PEG 400	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*, 40:231-242
39	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00032	-3.49	propylene glycol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*, 40:231-242
40	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.000287	-3.54	1-propanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*, 40:231-242
41	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00054	-3.27	ethanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*, 40:231-242
42	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00295	-2.53	methanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*, 40:231-242
43	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00417	-2.38	water	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*, 40:231-242
44	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00478	-2.32	water	dermatom. 0.32 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*, 40:231-242
45	theophylline	180.17	14.05	-0.39	4	1	0.000432	-3.36	water	dermatomed 0.2 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*, 40:231-242
46	mannitol	182.17	18.63	-3.01	6	6	0.000025	-4.60	dist. water	isol. epidermis	abdomen	flow-through	0.9% physiological saline	32	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 827-830

Group A5

Type of skin: human | Site: abdominal | 32 °C at the surface of the skin | Time of 24 -48 h | HPLC / GC / radiolabelled | Vehicle: water | propylene glycol | Receptor fluid | normal saline | HEPES-buffered Hanks´ balanced salt solution

Cell type: static | 37 °C in WB | UV / VS | physiological buffer | ethanol, methanol

No	Name	MW	SP (cal/cm^3)$^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	codeine	299.4	12.09	1.28	4	1	0.000049	-4.31	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	24	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6:825-832
2	coumarin	146.15	11.91	1.51	1	0	0.0091	-2.04	phosphate buffer (pH 7.4)	full-thickness	abdomen	static	phosphate buffer (pH 7.4)	37	48	radiolabelled (14C)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
3	etorphine	411.55	11.76	3.02	5	2	0.0036	-2.44	HCL & isotonic TRIS buffer	full-thickness	abdominal	static	isotonic TRIS buffer	37	24	radiolabelled (3H)	*Pharm.Res.*, 9: 963-965
4	griseofulvin	352.77	10.44	1.92	6	0	0.0013	-2.89	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
5	griseofulvin	352.77	10.44	1.92	6	0	0.00194	-2.71	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
6	nicotine	162.3	11.25	1	2	0	0.0103	-1.99	0.05M phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	0.05M phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
7	n-nitrosodiethanolamine	134.13	15.67	-1.28	4	2	0.0041	-2.39	isoprpyl myristate + sucrose (3H)	isol. epidermis	abdomen	static	PBS	32 (skin)	48	radiolabelled (14C)	*Food Chem.Toxicol.*,33:315-322
8	salicylic acid	138.1	14.39	2.24	2	2	0.0131	-1.89	phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
9	testosterone	288.4	10.66	3.27	2	1	0.005012	-2.30	0.05M phosphate buffer 20% ethanol	dermatom. 0.41 mm	abdomen / breast	static	0.05M phosphate buffer	32 (skin)	28	radiolabelled (14C)	*Eur.J.Pharm.Sci.*, 11:59-68
10	methyl parathion	263.21	10.45	2.75	1	0	0.000013	-4.87	acetone	full-thickness	abdomen	static	saline, 4%BSA & gentamycin sulphate	32 (skin)	48	gas chromatography	*Occup.Environ.Med.*,54:524-525
11	cimetidine	252.34	12.86	0.4	6	3	0.000038	-4.42	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32 (skin)	24	radiolabelled	*Eur.J.Pharm.Sci.*, 2006

12	adenosine	267.24	15.97	-1.05	9	4	0.000133	-3.88	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32 (skin)	24	UV / VS	*Eur.J.Pharm.Sci.*, 2006
13	deoxyadenosine	251.24	15.49	-0.55	8	3	0.000129	-3.89	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32 (skin)	24	UV / VS	*Eur.J.Pharm.Sci.*, 2006

Group A6

Type of skin: human | Site: abdominal / breast | 32 °C at the surface of the skin | Time of 24-48 h | HPLC / GC / radiolabelled | Vehicle: water | propylene glycol | Receptor fluid | normal saline | HEPES-buffered Hanks´ balanced salt solution

Cell type: static | 37 °C in WB | physiological buffer | ethanol, methanol

No	Name	MW	SP (cal/cm^3)$^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	codeine	299.4	12.09	1.28	4	1	0.000049	-4.31	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	24	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6:825-832
2	coumarin	146.15	11.91	1.51	1	0	0.0091	-2.04	phosphate buffer (pH 7.4)	full-thickness	abdomen	static	phosphate buffer (pH 7.4)	37	48	radiolabelled (14C)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
3	etorphine	411.55	11.76	3.02	5	2	0.0036	-2.44	HCL & isotonic TRIS buffer	full-thickness	abdominal	static	isotonic TRIS buffer	37	24	radiolabelled (3H)	*Pharm.Res.*, 9: 963-965
4	griseofulvin	352.77	10.44	1.92	6	0	0.0013	-2.89	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
5	griseofulvin	352.77	10.44	1.92	6	0	0.00194	-2.71	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
6	nicotine	162.3	11.25	1	2	0	0.0103	-1.99	0.05M phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	0.05M phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
7	n-nitrosodiethanolamine	134.13	15.67	-1.28	4	2	0.0041	-2.39	isoprpyl myristate + sucrose (3H)	isol. epidermis	abdomen	static	PBS	32 (skin)	48	radiolabelled (14C)	*Food Chem.Toxicol.*,33:315-322
8	salicylic acid	138.1	14.39	2.24	2	2	0.0131	-1.89	phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
9	testosterone	288.4	10.66	3.27	2	1	0.005012	-2.30	0.05M phosphate buffer 20% ethanol	dermatom. 0.41 mm	abdomen / breast	static	0.05M phosphate buffer	32 (skin)	28	radiolabelled (14C)	*Eur.J.Pharm.Sci.*, 11:59-68
10	lindane	290.83	8.54	4.26	0	0	0.0000059	-5.23	acetone	dermat. 0.23 mm	breast / abdomen	static	50% aq. ethanol	32 (skin)	24	gas chromatography	*Hum.Exp.Toxicol.*, 16: 652-657
11	methyl parathion	263.21	10.45	2.75	1	0	0.000013	-4.87	acetone	full-thickness	abdomen	static	saline, 4% BSA & gentamycin sulphate	32 (skin)	48	gas chromatography	*Occup.Environ.Med.*,54:524-525
12	nicorandil	211.18	14.40	0.43	3	1	0.000266	-3.58	water	full-thickness	breast	static	saline	37	32	HPLC	*J.Pharm.Sci.*, 7:231-236
13	cimetidine	252.34	12.86	0.4	6	3	0.000038	-4.42	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32 (skin)	24	radiolabelled	*Eur.J.Pharm.Sci.*, 2006
14	adenosine	267.24	15.97	-1.05	9	4	0.000133	-3.88	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32 (skin)	24	UV / VS	*Eur.J.Pharm.Sci.*, 2006
15	deoxyadenosine	251.24	15.49	-0.55	8	3	0.000129	-3.89	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32 (skin)	24	UV / VS	*Eur.J.Pharm.Sci.*, 2006

Group A7

Type of skin: human | Site: all types | 32 °C at the surface of the skin | Time of 24-72 h | Any analytical tool | Vehicle: water | propylene glycol | Receptor fluid | normal saline | HEPES-buffered Hanks´ balanced salt solution

Cell type: static | 37 °C in WB | physiological buffer | ethanol, methanol

No	Name	MW	SP (cal/cm^3)1/2	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	benzoic acid	122.1	11.94	1.87	1	1	0.025	-1.60	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*, 170:129-133
2	caffeine	194.2	32.83	0.16	4	0	0.000258	-3.59	water	isol. epidermis	upper leg	static	PBS	37	24	HPLC	*Int.J.Pharm.*, 182:41-47

No	Name	MW	SP (cal/cm^3)1/2	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
3	codeine	299.4	12.09	1.28	4	1	0.000049	-4.31	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	24	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6:825-832
4	coumarin	146.15	11.91	1.51	1	0	0.0091	-2.04	phosphate buffer (pH 7.4)	full-thickness	abdomen	static	phosphate buffer (pH 7.4)	37	48	radiolabelled (14C)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
5	coumarin	146.15	11.91	1.51	1	0	0.0125	-1.90	phosphate buffer (pH 7.4)	full-thickness	scalp	static	phosphate buffer (pH 7.4)	37	48	radiolabelled (14C)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
6	dichlofenac	296.16	11.13	4.02	2	2	0.001	-3.00	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*, 170:129-133
7	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00000477	-5.32	ethanol	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
8	doxycycline HCL	444.44	16.55	-1.36	9	6	0.000211	-3.68	2:1 ethanol : M840	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
9	doxycycline HCL	444.44	16.55	-1.36	9	6	0.000266	-3.58	1:1 ethanol : M840	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
10	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00253	-2.6	2:1 ethanol : M840	epidermis	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
11	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00252	-2.6	1:1 ethanol : M840	epidermis	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
12	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000136	-5.87	40% propylene glycol	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
13	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000306	-5.51	propylene glycol & dodecylazacycloheptan-2-one	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
14	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.0000026	-5.59	propylene glycol & 5% dimethylsulphoxide	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
15	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000338	-5.47	propylene glycol & sodium lauryl sulphate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
16	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000282	-5.55	propylene glycol & dodecyl-L-pyroglutamate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
17	etorphine	411.55	11.76	3.02	5	2	0.0036	-2.44	HCL & isotonic TRIS buffer	full-thickness	abdominal	static	isotonic TRIS buffer	37	24	radiolabelled (3H)	*Pharm.Res.*, 9: 963-965
18	griseofulvin	352.77	10.44	1.92	6	0	0.0013	-2.89	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
19	griseofulvin	352.77	10.44	1.92	6	0	0.00194	-2.71	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
20	hydromorphone	285.34	10.96	1.6	4	1	0.000015	-4.82	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	56	GLC with nitrogen selective detector	*Pharm.Res.*, 6: 825-832
21	ibuprofen	206.3	10.21	3.79	1	1	0.0363	-1.44	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
22	lindane	290.83	8.54	4.26	0	0	0.0000059	-5.23	acetone	dermat. 0.23 mm	breast / abdomen	static	50% aq. ethanol	32 (skin)	24	gas chromatography	*Hum.Exp.Toxicol.*, 16: 652-657
23	methyl nicotinate	137.14	11.80	0.64	2	0	0.00389	-2.41	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
24	methyl parathion	263.21	10.45	2.75	1	0	0.000013	-4.87	acetone	full-thickness	abdomen	static	saline, 4% BSA & gentamycin sulphate	32(skin)	48	gas chromatography	*Occup.Environ.Med.*,54:524-525
25	morphine	285.3	13.68	0.72	4	2	0.0000093	-5.03	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate phosphate buffer	37	52	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6: 825-832
26	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000581	-3.24	45% aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
27	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000598	-3.22	60 % aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
28	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000099	-4.00	90 % aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
29	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.0000632	-4.20	none	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
30	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00012	-3.92	60% aq. PEG 400	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221

No	Name	MW	SP (cal/cm^3)1/2	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
31	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000105	-3.98	75% aq. PEG 400	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
32	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00121	-2.92	30% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52:119-135
33	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.0004	-3.40	60% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52:119-135
34	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000016	-4.80	90% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52:119-135
35	naproxene	230.3	11.42	3.1	2	1	0.00288	-2.54	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
36	nicorandil	211.18	14.40	0.43	3	1	0.000266	-3.58	water	full-thickness	breast	static	saline	37	32	HPLC	*J.Pharm.Sci*., 7:231-236
37	nicotine	162.3	11.25	1	2	0	0.0103	-1.99	0.05M phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	0.05M phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm.Sci*., 11:59-68
38	nicotine	162.3	11.25	1	2	0	0.00331	-2.48	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
39	propoxur	209.25	10.31	1.9	2	1	0.0000288	-4.54	aq. methanol	full-thickness	abdomen	static	RPMI, L-glutamine, gentamycin & 10% foetal calf serum	37	22	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.*, 123:144-150
40	propoxur	209.25	10.31	1.9	2	1	0.0407	-1.39	aq. methanol	full-thickness	abdomen	static	RPMI, L-glutamine, gentamycin & 10% foetal calf serum	37	22	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.*, 123:144-150
41	salicylic acid	138.1	14.39	2.24	2	2	0.0131	-1.89	phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm.Sci*., 11:59-68
42	salicylic acid	138.1	14.39	2.24	2	2	0.0138	-1.86	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*, 170:129-133
43	testosterone	288.4	10.66	3.27	2	1	0.005012	-2.30	0.05M phosphate buffer 20% ethanol	dermatom. 0.41 mm	abdomen / breast	static	0.05M phosphate buffer	32 (skin)	28	radiolabelled (14C)	*Eur.J.Pharm.Sci*., 11:59-68
44	cimetidine	252.34	12.86	0.4	6	3	0.000038	-4.42	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32(skin)	24	radiolabelled	*Eur.J.Pharm.Sci*., 2006
45	adenosine	267.24	15.97	-1.05	9	4	0.000133	-3.88	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32(skin)	24	UV / VS	*Eur.J.Pharm.Sci*., 2006
46	deoxyadenosine	251.24	15.49	-0.55	8	3	0.000129	-3.89	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32 (skin)	24	UV / VS	*Eur.J.Pharm.Sci*., 2006

Group A8

Type of skin: human Site: all types 25-31° C WB Time Any analytical tool Vehicle: any Receptor fluid any

Cell type: flow-through / static

No	Name	MW	SP (cal/cm^3)$^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	chloroxylenol	156.6	11.20	3.25	1	1	0.05904	-1.23	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
2	resorcinol	110.11	15.18	1.03	2	2	0.00024	-3.62	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
3	salicylic acid	138.1	14.39	2.24	2	2	0.01194	-1.92	0.1M phosphate buffer (pH2)	full-thickness	breast	static	Tris.HCL buffer sol.	25	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418
4	salicylic acid	138.1	14.39	2.24	2	2	0.00074	-3.13	0.1M phosphate buffer (pH4)	full-thickness	breast	static	tris.HCL buffer sol.	25	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418
5	3,4 xylenol	202.55	11.54	2.61	1	1	0.036	-1.44	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
6	testosterone	288.4	10.66	3.27	2	1	0.0002399	-3.62	deionised	dermatom. 0.6 mm	not available	flow-through	PBS	27	48	radiolabelled (14C)	*J.Pharm.Sci*., 85:249-252
7	butyl paraben	194.23	11.45	3.47	2	1	0.056	-1.25	deionised water	epidermis	abdomen	static	PBS	30	4	HPLC	*Eur.J.Pharm.Sci*., 21:337-345

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
8	ethanol	46.07	10.92	-0.14	1	1	0.000317	-3.50	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol.*, 96: 921-925
9	hydroquinone	110.11	15.18	1.03	2	2	9.33E-06	-5.03	not available	isol. epidermis	abdomen	static	Dulbecco's PBS, antibiotics and fungicides	30	8	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016
10	mannitol	182.17	18.63	-3.01	6	6	0.000061	-4.21	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol.*, 96:921-925
11	methyl paraben	152.15	12.5	2	2	1	0.00943	-2.03	deionised water	epidermis	abdomen	static	PBS	30	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
12	paraquat	257.16	10.45	-2.71	0	0	0.0000087	-5.06	water	full-thickness	abdomen	static	static	30	6	radiolabelled (14C)	*J.Investig.Dermatol.*, 96:921-925
13	5-fluorouracil	130.01	13.46	-0.81	3	2	0.0000166	-4.78	0.002% aq. sodium azide solution	dermatomed 0.42 mm	abdomen	flow-through	0.002% aq. sodium azide solution	31	24	radiolabelled (3H)	*J.Investig.Pharmacol.*, 94:235-240

Group A9

Type of skin: human Site: all types 32° C WB Time Any analytical tool Vehicle: any Receptor fluid any

Cell type: flow-through / static

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	atenolol	266.3	12.49	-0.03	4	3	0.00005	-4.30	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
2	bisoprolol	325.5	10.01	1.84	5	2	0.00027	-3.57	Sorensen's phosphate buffer (pH7.4)	dermatom. 1.2 mm	abdominal	flow-through	normal saline	32	72	HPLC	*Int.J.Pharm.*, 173:141-148
3	celiprolol	379.5	11.51	1.93	5	3	0.00059	-3.23	Sorensen's phosphate buffer (pH7.4)	dermatom. 1.2 mm	abdominal	flow-through	normal saline	32	72	HPLC	*Int.J.Pharm.*, 173:141-148
4	clotrimazole	344.85	11.17	6.26	2	0	0.002	-2.70	propylene glycol	dermatom. 0.6 mm	abdomen	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*,215:51-56
5	b-estradiol	272.4	11.90	3.94	2	2	0.001	-3.00	75% ethanol	dermatomed 0.5 mm	abdomen	static	75% ethanol	32	60	radiolabelled (3H)	*Pharm.Res.*, 10:1745-1750
6	b-estradiol	272.4	11.90	3.94	2	2	0.01	-2.00	5% oleic acid, in 75% ethanol	dermatomed 0.5 mm	abdomen	static	5% oleic acid, in 75% ethanol	32	60	radiolabelled (3H)	*Pharm.Res.*, 10:1745-1750
7	2-ethoxyethanol	90.12	10.33	-0.42	2	1	0.000059	-4.23	methanol	dermat. 0.28 mm	breast	flow-through	MEM, sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl.Pharmacol.*, 180:74-82
8	2-ethoxyethanol	90.12	10.33	-0.42	2	1	0.000074	-4.13	methanol	dermat. 0.28 mm	breast	flow-through	MEM, sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl.Pharmacol.*, 180:74-82
9	flufenamic acid	281.2	10.96	4.88	5	2	0.0005209	-3.28	wool alcohols ointment	sc 0.012 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
10	flufenamic acid	281.2	10.96	4.88	5	2	0.0005407	-3.27	wool alcohols ointment	sc 0.012 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
11	flufenamic acid	281.2	10.96	4.88	5	2	0.0003889	-3.41	wool alcohols ointment	sc 0.012 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
12	flufenamic acid	281.2	10.96	4.88	5	2	0.0005499	-3.26	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
13	flufenamic acid	281.2	10.96	4.88	5	2	0.0005107	-3.29	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
14	flufenamic acid	281.2	10.96	4.88	5	2	0.0003798	-3.42	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
15	flufenamic acid	281.2	10.96	4.88	5	2	0.0000397	-4.40	wool alcohols ointment	full-thickness	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
16	flufenamic acid	281.2	10.96	4.88	5	2	0.0000929	-4.03	wool alcohols ointment	full-thickness	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
17	flufenamic acid	281.2	10.96	4.88	5	2	0.0000371	-4.43	wool alcohols ointment	full-thickness	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
18	hydrocortisone	362.5	12.75	1.61	5	3	0.0023	-2.64	propylene glycol	dermat. 0.6 mm	abdomen	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215:51-56

No	Name	MW	SP (cal/cm^3)$^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
19	mannitol	182.17	18.63	-3.01	6	6	0.000025	-4.60	dist. water	isol. epidermis	abdomen	flow-through	0.9% physiological saline	32	48	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
20	1-methoxylpropan-2-ol	90.12	10.16	-0.49	2	1	0.00144	-2.84	water	dermatom. 0.5 mm	breast	flow-through	Eagles MEM & sodium carbonate & gentamycin	32	24	radiolabelled (14C)	*Int.Arch.Occup.Environ.Health*, 75:519-527
21	1-methoxylpropan-2-ol	90.12	10.16	-0.49	2	1	0.000065	-4.19	none	dermatom. 0.5 mm	breast	flow-through	Eagles MEM & sodium carbonate & gentamycin	32	24	radiolabelled (14C)	*Int.Arch.Occup.Environ.Health*, 75:519-527
22	1-methoxylpropan-2-ol	90.12	10.16	-0.49	2	1	0.00065	-3.19	none	dermatom. 0.5 mm	breast	flow-through	Eagles MEM & sodium carbonate & gentamycin	32	24	radiolabelled (14C)	*Int.Arch.Occup.Environ.Health*, 75:519-527
23	metoprolol	267.4	10.39	1.69	4	2	0.00083	-3.08	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
24	naltrexone (NTX)	341	13.75	1.39	5	2	0.0095	-2.02	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
25	NTX-3-acetate (ACE-NTX)	383	12.96	1.47	5	1	0.0077	-2.11	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
26	NTX-3-propionate (PROP-NTX)	397	12.06	1.96	5	1	0.0025	-2.6	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
27	NTX-3-butyrate (BUT-NTX)	411	11.88	2.45	5	1	0.0013	-2.89	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
28	NTX-3-valerate (VAL-NTX)	425	11.72	2.45	5	1	0.0007	-3.15	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
29	NTX-3-hexanoate (HEX-NTX)	439	11.57	2.94	5	1	0.0012	-2.92	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
30	NTX-3 heptanoate (HEP-NTX)	453	11.44	3.92	5	1	0.0009	-3.05	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
31	oxprenolol	265.4	10.52	1.83	4	2	0.00154	-2.81	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
32	2-phenylphenol	170.21	12.24	3.28	1	1	0.0266	-1.58	60% aq. ethanol	isol. epidermis	dorsal / flank	static	saline (0.9% NaCL), 0.01% sodium azide & 3% BSA	32	8	radiolabelled (14C)	*Regul.Toxicol.Pharmacol.*, 35:198-208
33	2-phenylphenol	170.21	12.24	3.28	1	1	0.00159	-2.80	60% aq. ethanol	full-thickness	abdomen	static	Dulbecco's MEM, HEPES: Ham F-12, glutamx-I, BSA, L-glutamine, hydrocortisone & gentamycin	32	8	radiolabelled (14C)	*Regul.Toxicol.Pharmacol.*, 35:198-208
34	2-phenylphenol	170.21	12.24	3.28	1	1	0.0183	-1.74	60% aq. ethanol	isol. epidermis	abdomen	static	saline (0.9% NaCL), 0.01% sodium azide & 3% BSA	32	8	radiolabelled (14C)	*Regul.Toxicol.Pharmacol.*, 35:198-208
35	propranolol	295.3	11.13	2.6	3	2	0.00178	-2.75	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
36	propoxur	209.25	10.31	1.9	2	1	0.000885	-3.05	60% aq. ethanol	full-thickness	abdomen	static	culture medium & 10% fetal bovine serum	32	24	radiolabelled (14C)	*Toxicol.Sci.*, 58:15-22
37	salicylic acid	138.1	14.39	2.24	2	2	2.19	0.34	90% aq. propylene glycol	dermatom. 0.6 mm	abdomen	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215:51-56
38	terbinafine	291.4	9.33	5.81	1	0	0.001	-3.00	propylene glycol	dermatomed 0.6 mm	abdomen	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*,215: 51-56
39	testosterone	288.4	10.66	3.27	2	1	0.00012	-3.92	ethanol	full-thickness	abdomen	static	culture medium & 10% BSA	32	22	radiolabelled (14C)	*J.Control.Release*, 76: 327-335

Group A10

Type of skin: human Site: all types 37° C WB Time Any analytical tool Vehicle: any Receptor fluid any

Cell type: flow-through / static

No	Name	MW	SP (cal/cm^3)$^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	aniline	93	10.83	1.08	1	1	6.10E-02	-1.21	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
2	benzoic acid	122.1	11.94	1.87	1	1	0.025	-1.60	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.* 170: 129-133

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
3	benzoic acid	122.1	11.94	1.87	1	1	0.00133	-2.88	deionised water	dermatomed 0.6 mm	not available	flow-through	PBS	37	48	radiolabelled (14C)	*J.Pharm.Sci*., 85: 249-252
4	benzyl nicotinate	213.24	11.55	2.35	2	0	0.016	-1.80	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci*., 80: 54-56
5	benzyl nicotinate	213.24	11.55	2.35	2	0	2.04 E-05	-4.69	none	isol. epidermis	not available	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci*., 80: 54-56
6	4-n-butylaniline	149.24	9.51	3.1	1	1	0.411	-0.39	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
7	butyl paraben	194.23	11.45	3.47	2	1	0.0996	-1	deionised water	epidermis	abdomen	static	PBS	37	4	HPLC	*Eur.J.Pharm.Sci*., 21: 337-345
8	caffeine	194.2	32.83	0.16	4	0	0.000258	-3.59	water	isol. epidermis	upper leg	static	PBS	37	24	HPLC	*Int.J.Pharm*., 182: 41-47
9	codeine	299.4	12.09	1.28	4	1	0.000049	-4.31	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	24	GLC with nitrogen selective detector	*Pharmaceut.Res*., 6: 825-832
10	coumarin	146.15	11.91	1.51	1	0	0.0091	-2.04	phosphate buffer (pH 7.4)	full-thickness	abdomen	static	phosphate buffer (pH 7.4)	37	48	radiolabelled (14C)	*Meth. and Find Exp.Clin.Pharmacol*., 11: 643-646
11	coumarin	146.15	11.91	1.51	1	0	0.0125	-1.90	phosphate buffer (pH 7.4)	full-thickness	scalp	static	phosphate buffer (pH 7.4)	37	48	radiolabelled (14C)	*Meth. and Find Exp.Clin.Pharmacol*., 11: 643-646
12	diazinon	304.35	14.98	3.86	2	1	0.0095	-2.02	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, trizma, glucose	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8:1219-1224
13	dichlofenac	296.16	11.13	4.02	2	2	0.001	-3.00	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm*., 170:129-133
14	DDT	354.49	9.45	6.79	0	0	0.00594	-2.23	acetone	dermatomed 0.5 mm	abdomen	flow-through	Hanks HEPES buffered medium, 4% BSA & gentamycin	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 1225-1232
15	dimethylformamide	73.1	10.63	-0.93	1	0	0.0096	-2.02	none	full-thickness	abdomen	flow-through	physiological solution	37	4	gas chromatography	*Occup.Hyg*., 1: 191-198
16	2,4 dimethylamine	266.13	9.52	0.84	3	2	0.000945	-3.02	commercial formulation clean crop	dermatom.0.3 mm	abdomen	flow-through	HBSS, HEPES, buffer BSA & gentamycin sulphate	37	48	radiolabelled (14C)	*Toxicol.Vitro*,11: 251-262
17	2,4 dimethylamine	266.13	9.52	0.84	3	2	0.00081	-3.09	commercial formulation Wilbur Ellis	dermatom.0.3 mm	abdomen	flow-through	HBSS, HEPES, buffer BSA & gentamycin sulphate	37	48	radiolabelled (14C)	*Toxicol.Vitro*,11: 251-262
18	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00000477	-5.32	ethanol	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm*., 190: 155-164
19	doxycycline HCL	444.44	16.55	-1.36	9	6	0.000211	-3.68	2:1 ethanol : M840	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm*., 190: 155-164
20	doxycycline HCL	444.44	16.55	-1.36	9	6	0.000266	-3.58	1:1 ethanol : M840	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm*., 190: 155-164
21	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00253	-2.6	2:1 ethanol : M840	epidermis	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm*., 190: 155-164
22	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00252	-2.6	1:1 ethanol : M840	epidermis	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm*., 190: 155-164
23	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000136	-5.87	40% propylene glycol	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol*.,42: 468-472
24	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000306	-5.51	propylene glycol & dodecylazacycloheptan-2-one	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol*.,42: 468-472
25	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.0000026	-5.59	propylene glycol & 5% dimethylsulphoxide	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol*.,42: 468-472
26	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000338	-5.47	propylene glycol & sodium lauryl sulphate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol*.,42: 468-472
27	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000282	-5.55	propylene glycol & dodecyl-L-pyroglutamate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol*.,42: 468-472
28	b-estradiol	272.4	11.90	3.94	2	2	0.0041	-2.39	water	isol. epidermis	various	static	not available	37	not available	radiolabelled (3H)	*J.Pharm.Sci*., 84:1144-1146
29	etodolac	287.26	10.86	3.93	3	2	0.00746	-2.13	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Science*, 92:3:656-664
30	ethylaniline	121.2	9.73	2.11	1	1	0.288	-0.54	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
31	2-ethoxyethanol	90.12	10.33	-0.42	2	1	0.000882	-3.05	none	full-thickness	abdomen	flow-through	physiological solution	37	4	gas chromatography	*Occup.Hygiene*,1:191-198
32	etorphine	411.55	11.76	3.02	5	2	0.0036	-2.44	HCL & isotonic TRIS buffer	full-thickness	abdominal	static	isotonic TRIS buffer	37	24	radiolabelled (3H)	*Pharm.Res.*, 9: 963-965
33	famotidine	337.43	16.08	-0.64	5	4	0.000016	-4.79	not avialable	full-thickness	abdomen	franz	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
34	fentanyl	336.5	10.30	4.05	2	0	0.0056	-2.25	physiological buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	9	GCL with Nitrogen selective detector	*Pharm.Res.*, 6: 825-832
35	5-fluorouracil	130.01	13.46	-0.81	3	2	0.000601	-3.22	aq. buffered solution	epidermis	abdomen	static	buffered saline solution pH 7.4 + plysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
36	griseofulvin	352.77	10.44	1.92	6	0	0.0013	-2.89	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
37	griseofulvin	352.77	10.44	1.92	6	0	0.00194	-2.71	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
38	glyphosate	169.10	12.73	-4.47	3	4	0.000459	-3.34	water	dermatom. 1mm	not available	flow-through	PBS	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,34:731-735
39	n-hexyl nicotinate	207.27	10.49	3.1	2	0	0.0179	-1.75	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*,80:54-56
40	n-hexyl nicotinate	207.27	10.49	3.1	2	0	1.22E-05	-4.91	none	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*,80:54-56
41	hydrocortisone	362.5	12.75	1.61	5	3	0.000158	-3.80	Britton-Robinson 0.2M buffers & ethanol, pH1	full-thickness	abdomen	flow-through	solution of NaCl & sodium azide	37	28	HPLC	*J.Contr.Release*, 76:327-335
42	hydrocortisone	362.5	12.75	1.61	5	3	0.000075	-4.12	Britton-Robinson 0.2M buffers & ethanol, pH6	full-thickness	abdomen	flow-through	solution of NaCl & sodium azide	37	28	HPLC	*J.Contr.Release*, 76:327-335
43	hydrocortisone	362.5	12.75	1.61	5	3	0.000095	-4.02	Britton-Robinson 0.2M buffers & ethanol, pH10	full-thickness	abdomen	flow-through	solution of NaCl & sodium azide	37	28	HPLC	*J.Contr.Release*, 76:327-335
44	hydromorphone	285.34	10.96	1.6	4	1	0.000015	-4.82	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	56	GLC with nitrogen selective detector	*Pharm.Res.*, 6: 825-832
45	ibuprofen	206.3	10.21	3.97	1	1	0.0363	-1.44	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
46	ITF 1129	252	not calc.	2.41	not calc.	not calc.	0.01085	-1.96	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
47	ITF 296	238	12.91	1.61	3	0	0.00356	-2.45	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
48	isosorbide dinitrate (ISDN)	236.14	10.36	0.76	4	0	0.00449	-2.35	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
49	ketoprofen	254.29	11.75	3.12	2	1	0.00062	-3.21	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
50	lidocaine	234.34	8.78	1.66	2	1	0.000344	-3.46	40% propylene glycol & HCL (pH4)	dermat. 0.15 mm	leg	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (14C)	*Int.J.Pharm.*, 71:167-173
51	lidocaine	234.34	8.78	1.66	2	1	0.000388	-3.41	40% propylene glycol & HCL (pH6)	dermat. 0.15 mm	leg	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (14C)	*Int.J.Pharm.*, 71:167-173
52	lidocaine	234.34	8.78	1.66	2	1	0.0106	-1.97	40% propylene glycol & HCL (pH10)	dermat. 0.15 mm	leg	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (14C)	*Int.J.Pharm.*, 71:167-173
53	linoleic acid	289.45	9.05	7.51	1	1	0.0000106	-4.97	ethanol	full-thickness	abdomen	static	phosphate buffer, pluronic F88 & BHT	37	95	radiolabelled (14C)	*J.Pharm.Pharmacol.*, 34:610-611
54	malathion	330.36	10.61	2.29	2	0	0.203	-0.69	aq. ethanol	dermat. 1mm	not available	flow-through	PBS	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,34:731-735
55	methotrexate	454.45	15.05	-1.28	10	5	0.000318	-3.50	50% aq. propylene glycol	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm.*, 25:65-75
56	methotrexate	454.45	15.05	-1.28	10	5	0.000113	-3.95	0.03M HCL % aq. propylene glycol (pH 1.98)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm.*, 25:65-75
57	methotrexate	454.45	15.05	-1.28	10	5	0.000562	-3.25	0.001M KOH, 50% aq. propylene glycol (pH 4.12)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm.*, 25:65-75
58	methotrexate	454.45	15.05	-1.28	10	5	0.00113	-2.95	0.01M KOH, 50% aq. propylene glycol (pH 5.29)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm.*, 25:65-75

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
59	methotrexate	454.45	15.05	-1.28	10	5	0.00052	-3.28	0.05 M KOH, 50% aq. propylene glycol (pH 6.34)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm.*, 25:65-75
60	meperidine	247.4	9.82	3.03	2	0	0.0037	-2.43	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	8	GLC with nitrogen selective detector	*Pharm.Res.* 6:825-832
61	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.000025	-4.60	PEG 400	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*,40:231-242
62	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00032	-3.49	propylene glycol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40:231-242
63	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.000287	-3.54	1-propanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40:231-242
64	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00054	-3.27	ethanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40:231-242
65	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00295	-2.53	methanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*,40:231-242
66	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00417	-2.38	water	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*,40:231-242
67	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00478	-2.32	water	dermatom. 0.32 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*,40:231-242
68	methyl nicotinate	137.14	11.80	0.64	2	0	0.00389	-2.41	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
69	methyl nicotinate	137.14	11.80	0.64	2	0	0.00309	-2.51	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*,80:54-56
70	methyl nicotinate	137.14	11.80	0.64	2	0	0.0034	-2.47	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*,80:54-56
71	methyl paraben	152.15	12.5	2	2	1	0.0213	-1.67	deionised water	epidermis	abdomen	static	PBS	37	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
72	methyl paraben	152.15	12.5	2	2	1	0.00000589	-5.23	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci.*, 96, No. 4, 2007
73	morphine	285.3	13.68	0.72	4	2	0.0000093	-5.03	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate phosphate buffer	37	52	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6: 825-832
74	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00224	-2.65	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 7:141-148
75	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000581	-3.24	45% aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
76	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000598	-3.22	60 % aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
77	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000099	-4.00	90 % aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
78	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.0000632	-4.20	none	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
79	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00012	-3.92	60% aq. PEG 400	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
80	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000105	-3.98	75% aq. PEG 400	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
81	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00121	-2.92	30% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52:119-135
82	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.0004	-3.40	60% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52:119-135
83	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000016	-4.80	90% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52:119-135
84	naproxene	230.3	11.42	3.1	2	1	0.00288	-2.54	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
85	nicorandil	211.18	14.40	0.43	3	1	0.000266	-3.58	water	full-thickness	breast	static	saline	37	32	HPLC	*J.Pharm.Sci.*, 7:231-236
86	nicorandil	211.18	14.40	0.43	3	1	0.00005	-4.30	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11:59-68

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
87	nicotinic acid	123.11	13.23	0.69	2	1	0.000024	-4.62	water	isol. epidermis	abdomen / breast	static	isotonic PBS, NaCL	37	5	HPLC	*J.Pharm.Sci*., 80:104-107
88	nicotine	162.3	11.25	1	2	0	0.00331	-2.48	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
89	nimesulide	308.31	15.25	2.22	3	2	0.00101	-3	not avialable	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
90	nizatidine	331.45	12.36	-0.43	5	2	0.000038	-4.43	not avialable	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
91	parathion	291.26	10.76	3.73	1	0	0.000189	-3.72	none	dermatom. 0.5 mm	back	flow-through	Eagles-MEM-BSS & gentamycin	37	96	radiolabelled	*Toxicol.Appl.Pharmacol.*, 168:149-152
92	4-n-pentylaniline	163.3	9.79	3.59	1	1	0.226	-0.65	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
93	2-phenoxyethanol	138.17	11.49	1.1	2	1	0.001337	-2.87	methanol	dermat.0.33	breast / abdomen / leg	flow-through	MEM & penicillin / streptomycin +CO2	37	6	HPLC	*Food Chem.Toxicol.*,35:1009-1016
94	2-phenylethanol	122.2	11.38	1.57	1	1	0.031	-1.51	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
95	4-phenylbutanol	150	10.80	2.55	1	1	0.0862	-1.06	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
96	propoxur	209.25	10.31	1.9	2	1	0.0000288	-4.54	aq. methanol	full-thickness	abdomen	static	RPMI, L-glutamine, gentamycin & 10% foetal calf serum	37	22	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.*, 123:144-150
97	propoxur	209.25	10.31	1.9	2	1	0.0407	-1.39	aq. methanol	full-thickness	abdomen	static	RPMI, L-glutamine, gentamycin & 10% foetal calf serum	37	22	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.*, 123:144-150
98	ranitidine	314.1	11.41	0.29	5	2	0.0000887	-4.05	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
99	salicylic acid	138.1	14.39	2.24	2	2	0.00133	-2.88	not available	dermatom. 0.5 mm	breast	static	MEM, Ham's F-12, sodium bicarbonate, HEPES & gentamycin sulphate	37	12	radiolabelled (14C)	*J.Toxicol.: Cutaneous Ocul.Toxicol.*, 12:129-138
100	salicylic acid	138.1	14.39	2.24	2	2	0.00133	-2.88	not available	dermat. 0.5 mm	abdomen	static	MEM, Ham's F-12, sodium bicarbonate, HEPES & gentamycin sulphate	37	12	radiolabelled (14C)	*J.Toxicol.: Cutaneous Ocul.Toxicol.*, 12:129-138
101	salicylic acid	138.1	14.39	2.24	2	2	0.0138	-1.86	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*, 170:129-133
102	sufentanil	386.6	10.47	3.62	3	0	0.012	-1.92	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate phosphate buffer	37	8.5	GLC with nitrogen selective detector	*Pharm.Res*,6:825-832
103	testosterone	288.4	10.66	3.27	2	1	0.012	-1.92	0.1M phosphate buffer pH1	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
104	testosterone	288.4	10.66	3.27	2	1	0.0117	-1.93	0.1M phosphate buffer pH2	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
105	testosterone	288.4	10.66	3.27	2	1	0.00912	-2.04	hydrochloric acid and potassium chloride pH2	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
106	testosterone	288.4	10.66	3.27	2	1	0.012	-1.92	0.1M phosphate buffer pH6	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
107	testosterone	288.4	10.66	3.27	2	1	0.04	-1.40	0.1M phosphate buffer pH12	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
108	theophylline	180.17	14.05	-0.39	4	1	0.000432	-3.36	water	dermatomed 0.2 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem*., 40:231-242
109	triclosan	289.55	10.02	2.47	2	1	0.000034	-4.47	methanol and adhesive Durotak 387-2051	isol. epidermis	breast and abdomen	static	ethanol & PBS	37	12	HPLC	*Int.J.Pharm.*,235:229-236
110	androstedione	288.42	10.03	2.75	2	0	0.00124	-2.91	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
111	ethinyl estradiol	296.4	12.04	4	2	1	0.0000374	-4.43	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
112	prednisone	358.44	12.71	1.46	5	2	0.0000246	-4.61	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
113	prednisolone	360.44	12.96	1.49	5	3	0.0000235	-4.63	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
114	betamethasone	392.45	12.37	2.02	6	3	0.000002	-5.70	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273

No	Name	MW	SP (cal/cm^3)$^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
115	butyl paraben	194.23	11.45	3.47	2	1	0.056	-1.25	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci*., 96, No. 4, 2007

Group A11

Type of skin: human Site: all types All temperatures Time Any analytical tool Vehicle: any Receptor fluid any

Cell type: flow-through

No	Name	MW	SP (cal/cm^3)$^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	atenolol	266.3	12.49	-0.03	4	3	0.00005	-4.30	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm*., 194: 249-259
2	benzoic acid	122.1	11.94	1.87	1	1	0.00133	-2.88	deionised water	dermatomed 0.6 mm	not available	flow-through	PBS	37	48	radiolabelled (14C)	*J.Pharm.Sci*., 85:249-252
3	bisoprolol	325.5	10.01	1.84	5	2	0.00027	-3.57	Sorensen's phosphate buffer (pH7.4)	dermatom. 1.2 mm	abdominal	flow-through	normal saline	32	72	HPLC	*Int.J.Pharm*., 173:141-148
4	bisphenol A diglycidyl ether (BADGE)	340.8	10.38	3.84	4	0	4.80E-07	-6.32	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
5	borax	201.22	not calc.	not calc.	0	0	0.00017	-3.77	water	dermatom.0.5 mm	thigh	flow-through	PBS	32 (skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci*.,45:42-51
6	boric acid	61.83	44.06	-0.22	3	3	0.00029	-3.54	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32 (skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci*.,45:42-51
7	boric acid	61.83	44.06	-0.22	3	3	0.0000014	-5.85	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32 (skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci*.,45:42-51
8	boric acid	61.83	44.06	-0.22	3	3	0.00012	-3.92	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32 (skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci*.,45:42-51
9	boric acid	61.83	44.06	-0.22	3	3	0.0005	-3.30	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32 (skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci*.,45:42-51
10	caffeine	194.2	32.83	0.16	4	0	0.00072	-3.14	petrolatum	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol*., 115:1-11
11	caffeine	194.2	32.83	0.16	4	0	0.00062	-7.39	petrolatum	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol*., 115:1-11
12	caffeine	194.2	32.83	0.16	4	0	0.00021	-3.68	ethylene glycol	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol*., 115:1-11
13	caffeine	194.2	32.83	0.16	4	0	0.00051	-3.29	water gel	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol*., 115:1-11
14	cannabinol	310.46	10.9	7.23	2	1	0.00015	-3.82	propylene glycol : water (7:3) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol*., 56: 291-297
15	cannabidiol	314.46	11.11	8.01	2	2	0.00024	-3.62	propylene glycol : water (7:3) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol*., 56: 291-297
16	celiprolol	379.5	11.51	1.93	5	3	0.00059	-3.23	Sorensen's phosphate buffer (pH7.4)	dermatom. 1.2 mm	abdominal	flow-through	normal saline	32	72	HPLC	*Int.J.Pharm*., 173:141-148
17	chlorpyrifos	350.59	10.10	4.66	1	0	0.00025	-3.60	commercial solution containing xylene & 111-TCE	full-thickness	breast	flow-through	50% aq. ethanol	32 (skin)	24	gas chromatography	*Hum.Exp.Toxicol*,19:104-107
18	chlorpyrifos	350.59	10.10	4.66	1	0	0.00011	-3.96	ethanol	full-thickness	breast	flow-through	50% aq. ethanol	32 (skin)	24	gas chromatography	*Hum.Exp.Toxicol*,19:104-107
19	coumarin	146.15	11.91	1.51	1	0	0.000376	-3.42	ethanol	full-thickness	breast	flow-through	HEPES buffered HBSS & 0.5% gentamycin	32 (skin)	72	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.* 145:34-42
20	coumarin	146.15	11.91	1.51	1	0	0.000719	-3.14	ethanol	full-thickness	breast	flow-through	HEPES buffered HBSS & 0.5% gentamycin	32 (skin)	72	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.* 145:34-42
21	o-cresyl glycidyl ether (oCGE)	164.2	10.38	2.16	2	0	9.30E-05	-4.03	acetone	dermatommed	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*,30:469-483
22	diazinon	304.35	14.98	3.86	2	1	0.0095	-2.02	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, trizma, glucose	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8:1219-1224
23	DDT	354.49	9.45	6.79	0	0	0.00594	-2.23	acetone	dermatomed 0.5 mm	abdomen	flow-through	Hanks HEPES buffered medium, 4% BSA & gentamycin	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 1225-1232

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
24	dimethylformamide	73.1	10.63	-0.93	1	0	0.0096	-2.02	none	full-thickness	abdomen	flow-through	physiological solution	37	4	gas chromatography	*Occup.Hyg.*, 1:191-198
25	2,4 dimethylamine	266.13	9.52	0.84	3	2	0.000945	-3.02	commercial formulation clean crop	dermatom.0.3 mm	abdomen	flow-through	HBSS, HEPES, buffer BSA & gentamycin sulphate	37	48	radiolabelled (14C)	*Toxicol.Vitro*,11:251-262
26	2,4 dimethylamine	266.13	9.52	0.84	3	2	0.00081	-3.09	commercial formulation Wilbur Ellis	dermatom.0.3 mm	abdomen	flow-through	HBSS, HEPES, buffer BSA & gentamycin sulphate	37	48	radiolabelled (14C)	*Toxicol.Vitro*,11:251-262
27	disodium octaborate tetrahydrate	412.52	28	not calc.	28	12	8.00E-05	-4.10	water	dermat.0.5 mm	thigh	flow-through	PBS	32 (skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
28	dodecyl glycidyl ether (C12GE)	242.2	8.41	5.01	2	0	0.00000331	-5.48	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
29	epikote YX4000	354.4	11.00	5.19	4	0	0.000000047	-7.33	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
30	2-ethoxyethanol	90.12	10.33	-0.42	2	1	0.000882	-3.05	none	full-thickness	abdomen	flow-through	physiological solution	37	4	gas chromatography	*Occup.Hygiene*,1:191-198
31	2-ethoxyethanol	90.12	10.33	-0.42	2	1	0.000059	-4.23	methanol	dermat. 0.28 mm	breast	flow-through	MEM, sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl.Pharmacol.*, 180:74-82
32	2-ethoxyethanol	90.12	10.33	-0.42	2	1	0.000074	-4.13	methanol	dermat. 0.28 mm	breast	flow-through	MEM, sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl.Pharmacol.*, 180:74-82
33	flufenamic acid	281.2	10.96	4.88	5	2	0.0005209	-3.28	wool alcohols ointment	sc 0.012 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
34	flufenamic acid	281.2	10.96	4.88	5	2	0.0005407	-3.27	wool alcohols ointment	sc 0.012 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
35	flufenamic acid	281.2	10.96	4.88	5	2	0.0003889	-3.41	wool alcohols ointment	sc 0.012 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
36	flufenamic acid	281.2	10.96	4.88	5	2	0.0005499	-3.26	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
37	flufenamic acid	281.2	10.96	4.88	5	2	0.0005107	-3.29	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
38	flufenamic acid	281.2	10.96	4.88	5	2	0.0003798	-3.42	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
39	flufenamic acid	281.2	10.96	4.88	5	2	0.0000397	-4.40	wool alcohols ointment	full-thickness	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
40	flufenamic acid	281.2	10.96	4.88	5	2	0.0000929	-4.03	wool alcohols ointment	full-thickness	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
41	flufenamic acid	281.2	10.96	4.88	5	2	0.0000371	-4.43	wool alcohols ointment	full-thickness	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
42	5-fluorouracil	130.01	13.46	-0.81	3	2	0.0000166	-4.78	0.002% aq. sodium azide solution	dermatomed 0.42 mm	abdomen	flow-through	0.002% aq. sodium azide solution	31	24	radiolabelled (3H)	*J.Investig.Pharmacol.*, 94:235-240
43	glyphosate	169.10	12.73	-4.47	3	4	0.000459	-3.34	water	dermatom. 1mm	not available	flow-through	PBS	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,34:731-735
44	1,6-hexanediol diglycidyl ether (HDDGE)	230.2	9.36	0.84	4	0	0.000136	-3.87	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
45	hydrocortisone	362.5	12.75	1.61	5	3	0.000158	-3.80	Britton-Robinson 0.2M buffers & ethanol, pH1	full-thickness	abdomen	flow-through	solution of NaCl & sodium azide	37	28	HPLC	*J.Contr.Release*, 76:327-335
46	hydrocortisone	362.5	12.75	1.61	5	3	0.000075	-4.12	Britton-Robinson 0.2M buffers & ethanol, pH6	full-thickness	abdomen	flow-through	solution of NaCl & sodium azide	37	28	HPLC	*J.Contr.Release*, 76:327-335
47	hydrocortisone	362.5	12.75	1.61	5	3	0.000095	-4.02	Britton-Robinson 0.2M buffers & ethanol, pH10	full-thickness	abdomen	flow-through	solution of NaCl & sodium azide	37	28	HPLC	*J.Contr.Release*, 76:327-335
48	ITF 1129	252	not calc.	1.61	not calc.	not calc.	0.01085	-1.96	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
49	ITF 296	238	12.91	1.61	3	0	0.00356	-2.45	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
50	isosorbide dinitrate (ISDN)	236.14	10.36	0.76	4	0	0.00449	-2.35	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
51	lidocaine	234.34	8.78	1.66	2	1	0.000344	-3.46	40% propylene glycol & HCL (pH4)	dermat. 0.15 mm	leg	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (14C)	*Int.J.Pharm.*, 71:167-173

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
52	lidocaine	234.34	8.78	1.66	2	1	0.000388	-3.41	40% propylene glycol & HCL (pH6)	dermat. 0.15 mm	leg	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (14C)	*Int.J.Pharm.*, 71:167-173
53	lidocaine	234.34	8.78	1.66	2	1	0.0106	-1.97	40% propylene glycol & HCL (pH10)	dermat. 0.15 mm	leg	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (14C)	*Int.J.Pharm.*, 71:167-173
54	malathion	330.36	10.61	2.29	2	0	0.203	-0.69	aq. ethanol	dermat. 1mm	not available	flow-through	PBS	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,34:731-735
55	mannitol	182.17	18.63	-3.01	6	6	0.000025	-4.60	dist. water	isol. epidermis	abdomen	flow-through	0.9% physiological saline	32	48	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
56	mannitol	182.17	18.63	-3.01	6	6	0.000025	-4.60	dist. water	dermat.0.13 mm	abdomen	flow-through	0.9% physiological saline	not available	not available	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
57	methiocarb	225.31	10.92	2.87	1	1	0.0011	-2.96	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*,48:697-701
58	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.000025	-4.60	PEG 400	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*,40:231-242
59	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00032	-3.49	propylene glycol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40:231-242
60	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.000287	-3.54	1-propanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40:231-242
61	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00054	-3.27	ethanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40:231-242
62	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00295	-2.53	methanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*,40:231-242
63	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00417	-2.38	water	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*,40:231-242
64	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00478	-2.32	water	dermatom. 0.32 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*,40:231-242
65	1-methoxylpropan-2-ol	90.12	10.16	-0.49	2	1	0.00144	-2.84	water	dermatom. 0.5 mm	breast	flow-through	Eagles MEM & sodium carbonate & gentamycin	32	24	radiolabelled (14C)	*Int.Arch.Occup.Environ.Health*, 75:519-527
66	1-methoxylpropan-2-ol	90.12	10.16	-0.49	2	1	0.000065	-4.19	none	dermatom. 0.5 mm	breast	flow-through	Eagles MEM & sodium carbonate & gentamycin	32	24	radiolabelled (14C)	*Int.Arch.Occup.Environ.Health*, 75:519-527
67	1-methoxylpropan-2-ol	90.12	10.16	-0.49	2	1	0.00065	-3.19	none	dermatom. 0.5 mm	breast	flow-through	Eagles MEM & sodium carbonate & gentamycin	32	24	radiolabelled (14C)	*Int.Arch.Occup.Environ.Health*, 75:519-527
68	metoprolol	267.4	10.39	1.69	4	2	0.00083	-3.08	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
69	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00224	-2.65	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 7:141-148
70	naltrexone (NTX)	341	13.75	1.39	5	2	0.0095	-2.02	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
71	NTX-3-acetate (ACE-NTX)	383	12.96	1.47	5	1	0.0077	-2.11	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
72	NTX-3-propionate (PROP-NTX)	397	12.06	1.96	5	1	0.0025	-2.6	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
73	NTX-3-butyrate (BUT-NTX)	411	11.88	2.45	5	1	0.0013	-2.89	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
74	NTX-3-valerate (VAL-NTX)	425	11.72	2.45	5	1	0.0007	-3.15	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
75	NTX-3-hexanoate (HEX-NTX)	439	11.57	2.94	5	1	0.0012	-2.92	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
76	NTX-3 heptanoate (HEP-NTX)	453	11.44	3.92	5	1	0.0009	-3.05	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
77	nicorandil	211.18	14.40	0.43	3	1	0.00005	-4.30	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
78	oxprenolol	265.4	10.52	1.83	4	2	0.00154	-2.81	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
79	parathion	291.26	10.76	3.73	1	0	0.000189	-3.72	none	dermatom. 0.5 mm	back	flow-through	Eagles-MEM-BSS & gentamycin	37	96	radiolabelled	*Toxicol.Appl.Pharmacol.*, 168:149-152

No	Name	MW	SP (cal/cm^3)$^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
80	2-phenoxyethanol	138.17	11.49	1.1	2	1	0.001337	-2.87	methanol	dermat.0.33	breast / abdomen / leg	flow-through	MEM & penicillin / streptomycin +CO2	37	6	HPLC	*Food Chem.Toxicol.*,35:1009-1016
81	pirimicarb	238.29	11.05	1.4	4	0	0.0027	-2.57	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*,48:697-701
82	prochloraz	376.7	10.69	4.13	3	0	0.0007	-3.15	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*,48:697-701
83	propranolol	295.3	11.13	2.6	3	2	0.00178	-2.75	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
84	testosterone	288.4	10.66	3.27	2	1	0.012	-1.92	0.1M phosphate buffer pH1	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
85	testosterone	288.4	10.66	3.27	2	1	0.0117	-1.93	0.1M phosphate buffer pH2	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
86	testosterone	288.4	10.66	3.27	2	1	0.00912	-2.04	hydrochloric acid and potassium chloride pH2	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
87	testosterone	288.4	10.66	3.27	2	1	0.012	-1.92	0.1M phosphate buffer pH6	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
88	testosterone	288.4	10.66	3.27	2	1	0.04	-1.40	0.1M phosphate buffer pH12	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
89	testosterone	288.4	10.66	3.27	2	1	0.0000267	-4.57	ethanol	dermatom. 0.28 mm	breast	flow-through	Eagles MEM & 2% PEG (pH 7.4)	32 (not available)	24	radiolabelled (14C)	*Toxicology*, 168:63
90	testosterone	288.4	10.66	3.27	2	1	0.00028	-3.55	petrolatum	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115:1-11
91	testosterone	288.4	10.66	3.27	2	1	0.00018	-3.74	ethylene glycol	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115:1-11
92	testosterone	288.4	10.66	3.27	2	1	0.00671	-2.17	water gel	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115:1-11
93	testosterone	288.4	10.66	3.27	2	1	0.0002399	-3.62	deionised	dermatom. 0.6 mm	not available	flow-through	PBS	27	48	radiolabelled (14C)	*J.Pharm.Sci.*, 85:249-252
94	Δ-tetrahydrocannabinol (THC)	314.46	9.75	7.6	2	1	0.000028	-4.55	propylene glycol : water : ethanol (9:1:1) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol.*, 56: 291-297
95	theophylline	180.17	14.05	-0.39	4	1	0.000432	-3.36	water	dermatomed 0.2 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*, 40:231-242
96	water	18.02	26.68	-1.38	1	1	0.0013	-2.89	none	dermatomed 0.42 mm	abdomen	flow-through	0.002% sodium azide solution	31 (skin)	6	radiolabelled (3H)	*J.Invest.Dermatol.*, 94:235-240

Group A12

Type of skin: human Site: all types All temperatures Time Any analytical tool Vehicle: any Receptor flluid any

Cell type: static

No	Name	MW	SP (cal/cm^3)$^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	aldosterone	360.45	12.31	1.63	4	2	3.00E-06	-5.52	water	isol. epidermis	not given	static	aq. penecillin / streptomycin	26 (not available)	not available	radiolabelled	*J.Invest.Dermatol.*, 52-63-70
2	aldosterone	360.45	12.31	1.63	4	2	5.80E-05	-4.24	not available	isol. epidermis	various	static	not available	26 (not available)	not available	radiolabelled	*J.Pharm.Sci.*, 84:1144-1146
3	aniline	93	10.83	1.08	1	1	6.10E-02	-1.21	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
4	benzene	78.115	9.19	1.99	0	0	0.111	-0.95	water	isol. epidermis	abdomen	static	0.1% NaCL solution	31 (skin)	4	HPLC	*J.Invest.Dermatol.*,85: 522-526
5	benzene	78.12	9.19	1.99	0	0	0.00094	-3.03	hexodecane	isol. epidermis	abdomen	static	0.1% NaCL solution	31 (skin)	0	HPLC	*J.Invest.Dermatol.*,85: 522-526
6	benzene	78.12	9.19	1.99	0	0	0.1665	-0.78	isoctane	isol. epidermis	abdomen	static	0.1% NaCL solution	31 (skin)	0	HPLC	*J.Invest.Dermatol.*,85: 522-526

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
7	benzene	78.12	9.19	1.99	0	0	0.0024	-2.62	isoctane	isol. epidermis	abdomen	static	0.1% NaCL solution	31 (skin)	0	HPLC	*J.Invest.Dermatol.*,85: 522-526
8	benzene	78.12	9.19	1.99	0	0	0.00011	-3.96	isoctane	isol. epidermis	abdomen	static	0.1% NaCL solution	31 (skin)	0	HPLC	*J.Invest.Dermatol.*,85: 522-526
9	benzoic acid	122.1	11.94	1.87	1	1	0.025	-1.60	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.* 170:129-133
10	benzyl nicotinate	213.24	11.55	2.35	2	0	0.016	-1.80	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*, 80:54-56
11	benzyl nicotinate	213.24	11.55	2.35	2	0	2.04 E-05	-4.69	none	isol. epidermis	not available	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*, 80:54-56
12	4-bromophenol	173.01	11.48	2.4	1	1	0.03612	-1.44	dist. water	isol. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
13	4-n-butylaniline	149.24	9.51	3.1	1	1	0.41	-0.39	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36		*I.J.Pharmac.*, 129: 33-40
14	butyl nicotinate	179.22	10.57	2.11	2	0	0.0166	-1.78	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37 (not available)	5	HPLC	*J.Pharm.Sci.*, 80:54-56
15	butyl nicotinate	179.22	10.57	2.11	2	0	0.000079	-4.1	none	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37 (not available)	5	HPLC	*J.Pharm.Sci.*, 80:54-56
16	butyl paraben	194.23	11.45	3.47	2	1	0.0277	-1.56	deionised water	epidermis	abdomen	static	PBS	23	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
17	butyl paraben	194.23	11.45	3.47	2	1	0.056	-1.25	deionised water	epidermis	abdomen	static	PBS	30	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
18	butyl paraben	194.23	11.45	3.47	2	1	0.0996	-1	deionised water	epidermis	abdomen	static	PBS	37	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
19	butyl paraben	194.23	11.45	3.47	2	1	0.275	-0.56	deionised water	epidermis	abdomen	static	PBS	45	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
20	2-butoxyethanol	118.18	9.88	0.57	2	1	0.000214	-3.67	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
21	2-(2-butoxyethoxy) ethanol	162.23	9.74	0.29	3	1	0.0000357	-4.45	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
22	caffeine	194.2	32.83	0.16	4	0	0.000258	-3.59	water	isol. epidermis	upper leg	static	PBS	37	24	HPLC	*Int.J.Pharm.*, 182:41-47
23	chloroxylenol	156.6	11.20	3.25	1	1	0.05904	-1.23	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
24	clotrimazole	344.85	11.17	6.26	2	0	0.002	-2.70	propylene glycol	dermatom. 0.6 mm	abdomen	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215:51-56
25	codeine	299.4	12.09	1.28	4	1	0.000049	-4.31	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	24	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6:825-832
26	cortexolone	346.47	11.91	3.15	4	2	0.000075	-4.12	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52:63-70
27	corticosterone	346.5	11.91	1.99	4	2	0.00006	-4.22	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52:63-70
28	cortisone	360.5	12.1	1.81	5	2	0.00001	-5.00	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52:63-70
29	coumarin	146.15	11.91	1.51	1	0	0.0091	-2.04	phosphate buffer (pH 7.4)	full-thickness	abdomen	static	phosphate buffer (pH 7.4)	37	48	radiolabelled (14C)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
30	coumarin	146.15	11.91	1.51	1	0	0.0125	-1.90	phosphate buffer (pH 7.4)	full-thickness	scalp	static	phosphate buffer (pH 7.4)	37	48	radiolabelled (14C)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
31	2-cresol (o-cresol)	108.1	11.89	2.06	1	1	0.01572	-1.80	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
32	3-cresol (m-cresol)	108.14	11.89	2.06	1	1	0.01524	-1.82	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
33	4-cresol (p-cresol)	108.1	11.89	2.06	1	1	0.01752	-1.76	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
34	dichlofenac	296.16	11.13	4.02	2	2	0.001	-3.00	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*, 170:129-133

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
35	DEHP	390.57	9.39	8.39	2	0	0.0000057	-5.24	none	isol. epidermis	abdomen	static	50% aq. ethanol	30 (not available)	72	radiolabelled (14C)	*Environ.Health Perspect.*, 74:223-227
36	DEP	222.24	10.51	2.65	2	0	0.0000114	-4.94	none	isol. epidermis	abdomen	static	50% aq. ethanol	30 (not available)	30	radiolabelled (14C)	*Environ.Health Perspect.*, 74:223-227
37	dibutyl squarate	226.27	10.58	2.45	4	0	0.00002	-4.70	acetone	dermatomed skin	thigh	static	buffer	not given	48	UV spectroscopy	*Arch.Dermatol.Res.*, 280:57-60
38	dibutylphthalate	278.35	10.86	5.11	2	0	0.0000023	-5.64	none	isol. epidermis	abdomen	static	50% aq. ethanol	30 (not available)	30	radiolabelled (14C)	*Environ.Health Perspect.*, 74:223-227
39	diethyl squarate	170.16	11.50	4.07	4	0	0.00012	-3.92	acetone	dermatomed skin	thigh	static	buffer	not available	48	UV spectroscopy	*Arch.Dermatol.Res.*, 280:57-60
40	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00000477	-5.32	ethanol	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
41	doxycycline HCL	444.44	16.55	-1.36	9	6	0.000211	-3.68	2:1 ethanol : M840	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
42	doxycycline HCL	444.44	16.55	-1.36	9	6	0.000266	-3.58	1:1 ethanol : M840	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
43	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00253	-2.6	2:1 ethanol : M840	epidermis	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
44	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00252	-2.6	1:1 ethanol : M840	epidermis	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
45	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000136	-5.87	40% propylene glycol	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
46	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000306	-5.51	propylene glycol & dode-cylazacycloheptan-2-one	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
47	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.0000026	-5.59	propylene glycol & 5% dimethylsulphoxide	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
48	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000338	-5.47	propylene glycol & sodium lauryl sulphate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
49	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000282	-5.55	propylene glycol & dodecyl-L-pyroglutamate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
50	b-estradiol	272.4	11.90	3.94	2	2	0.0003	-3.52	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52: 63-70
51	b-estradiol	272.4	11.90	3.94	2	2	0.001	-3.00	75%ethanol	dermatomed 0.5 mm	abdomen	static	75% ethanol	32	60	radiolabelled (3H)	*Pharm.Res.*, 10:1745-1750
52	b-estradiol	272.4	11.90	3.94	2	2	0.01	-2.00	5% oleic acid, in 75% ethanol	dermatomed 0.5 mm	abdomen	static	5% oleic acid, in 75% ethanol	32	60	radiolabelled (3H)	*Pharm.Res.*, 10:1745-1750
53	b-estradiol	272.4	11.90	3.94	2	2	0.0041	-2.39	water	isol. epidermis	various	static	not available	37	not available	radiolabelled (3H)	*J.Pharm.Sci.*, 84:1144-1146
54	estriol	288.4	12.95	2.81	3	3	0.00004	-4.40	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52: 63-70
55	estrone	270.4	11.55	3.43	2	1	0.0036	-2.44	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52: 63-70
56	ethanol	46.07	10.92	-0.14	1	1	0.000317	-3.50	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol.*, 96: 921-925
57	etodolac	287.26	10.86	3.93	3	2	0.00746	-2.13	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
58	ethylaniline	121.2	9.73	2.11	1	1	0.288	-0.54	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
59	ethyl nicotinate	151.17	11.06	1.13	2	2	0.00608	-2.22	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37(not available)	5	HPLC	*J.Pharm.Sci.*, 80:54-56
60	ethyl nicotinate	151.17	11.06	1.13	2	2	0.0066	-2.18	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37(not available)	5	HPLC	*J.Pharm.Sci.*, 80:54-56
61	ethyl nicotinate	151.17	11.06	1.13	2	2	0.000216	-3.65	none	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37(not available)	5	HPLC	*J.Pharm.Sci.*, 80:54-56
62	2-ethoxyethanol	90.12	10.33	-0.42	2	1	0.000842	-3.07	none	full-thickness	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
63	2-(2-ethoxyethoxy) ethanol	134.18	10.04	-0.69	3	1	0.000132	-3.88	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
64	2-ethoxyethyl acetate	132.16	9.22	0.59	2	0	0.000807	-3.09	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
65	etorphine	411.55	11.76	3.02	5	2	0.0036	-2.44	HCL & isotonic TRIS buffer	full-thickness	abdominal	static	isotonic TRIS buffer	37	24	radiolabelled (3H)	*Pharm.Res.*, 9: 963-965
66	famotidine	337.43	16.08		5	4	0.000016	-4.79	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
67	fentanyl	336.5	10.30	3.89	2	0	0.0056	-2.25	physiological buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	9	GCL with Nitrogen selective detector	*Pharm.Res.*, 6: 825-832
68	5-fluorouracil	130.01	13.46	-0.81	3	2	0.000601	-3.22	aq. buffered solution	epidermis	abdomen	static	buffered saline solution pH 7.4 + plysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
69	griseofulvin	352.77	10.44	1.92	6	0	0.0013	-2.89	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
70	griseofulvin	352.77	10.44	1.92	6	0	0.00194	-2.71	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
71	n-hexyl nicotinate	207.27	10.49	3.1	2	0	0.0179	-1.75	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*,80:54-56
72	n-hexyl nicotinate	207.27	10.49	3.1	2	0	1.22E-05	-4.91	none	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*,80:54-56
73	hydrocortisone	362.5	12.75	1.61	5	3	0.0023	-2.64	propylene glycol	dermat. 0.6 mm	abdomen	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215:51-56
74	hydrocortisone	362.5	12.75	1.61	5	3	0.000003	-5.52	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)		radiolabelled	*J.Investig.Dermatol.*, 52: 63-70
75	hydromorphone	285.34	10.96	1.6	4	1	0.000015	-4.82	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	56	GLC with nitrogen selective detector	*Pharm.Res.*, 6: 825-832
76	hydroquinone	110.11	15.18	1.03	2	2	9.33E-06	-5.03	not available	isol. epidermis	abdomen	static	Dulbecco's PBS, antibiotics and fungicides	30	8	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016
77	ibuprofen	206.3	10.21	3.79	1	1	0.0363	-1.44	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
78	ketoprofen	254.29	11.75	0.97	2	1	0.00062	-3.21	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
79	lindane	290.83	8.54	4.26	0	0	0.0000059	-5.23	acetone	dermat. 0.23 mm	breast / abdomen	static	50% aq. ethanol	32 (skin)	6	gas chromatography	*Hum.Exp.Toxicol.*, 16: 652-657
80	lindane	290.83	8.54	4.26	0	0	0.0000059	-5.23	acetone	dermat. 0.23 mm	breast / abdomen	static	50% aq. ethanol	32 (skin)	24	gas chromatography	*Hum.Exp.Toxicol.*, 16: 652-657
81	linoleic acid	289.45	9.05	7.51	1	1	0.0000106	-4.97	ethanol	full-thickness	abdomen	static	phosphate buffer, pluronic F88 & BHT	37	95	radiolabelled (14C)	*J.Pharm.Pharmacol.*, 34:610-611
82	mannitol	182.17	18.63	-3.01	6	6	0.000011	-4.96	dist. water	full-thickness	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
83	mannitol	182.17	18.63	-3.01	6	6	0.000011	-4.96	dist. water	isol. epidermis	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
84	mannitol	182.17	18.63	-3.01	6	6	0.000061	-4.21	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol.*, 96:921-925
85	methanol	32.04	11.68	-0.84	1	1	0.0016	-2.80	water	stratum corneum membrane	abdomen	static	WATER	22 (not available)	48	radiolabelled	*Int.J.Pharm.*, 18: 299-309
86	methotrexate	454.45	15.05	-1.28	10	5	0.000318	-3.50	50% aq. propylene glycol	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm.*, 25:65-75
87	methotrexate	454.45	15.05	-1.28	10	5	0.000113	-3.95	0.03M HCL % aq. propylene glycol (pH 1.98)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm.*, 25:65-75
88	methotrexate	454.45	15.05	-1.28	10	5	0.000562	-3.25	0.001M KOH, 50% aq. propylene glycol (pH 4.12)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm.*, 25:65-75
89	methotrexate	454.45	15.05	-1.28	10	5	0.00113	-2.95	0.01M KOH, 50% aq. propylene glycol (pH 5.29)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm.*, 25:65-75
90	methotrexate	454.45	15.05	-1.28	10	5	0.00052	-3.28	0.05 M KOH, 50% aq. propylene glycol (pH 6.34)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm.*, 25:65-75

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
91	meperidine	247.4	9.82	3.03	2	0	0.0037	-2.43	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	8	GLC with nitrogen selective detector	*Pharm.Res.* 6:825-832
92	methyl nicotinate	137.14	11.80	0.64	2	0	0.00389	-2.41	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
93	methyl nicotinate	137.14	11.80	0.64	2	0	0.00309	-2.51	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*,80:54-56
94	methyl nicotinate	137.14	11.80	0.64	2	0	0.0034	-2.47	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*,80:54-56
95	methyl parathion	263.21	10.45	2.75	1	0	0.000013	-4.87	acetone	full-thickness	abdomen	static	saline, 4%BSA & gentamycin sulphate	32 (skin)	48	gas chromatography	*Occup.Environ.Med.*,54:524-525
96	methyl parathion	263.21	10.45	2.75	1	0	0.000038	-4.42	20% MPA, 75% xylene, 5% dispersing agents	full-thickness	abdomen	static	saline, 4% BSA & gentamycin sulphate	32 (skin)	48	gas chromatography	*Occup.Environ.Med.*,54:524-525
97	methyl paraben	152.15	12.5	2	2	1	0.00418	-2.38	deionised water	epidermis	abdomen	static	PBS	23	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
98	methyl paraben	152.15	12.5	2	2	1	0.00943	-2.03	deionised water	epidermis	abdomen	static	PBS	30	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
99	methyl paraben	152.15	12.5	2	2	1	0.0213	-1.67	deionised water	epidermis	abdomen	static	PBS	37	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
100	methyl paraben	152.15	12.5	2	2	1	0.032	-1.49	deionised water	epidermis	abdomen	static	PBS	45	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
101	2-methoxyethanol	76.1	10.67	-0.91	2	1	0.00289	-2.54	none	isol. epidermis	abdomen	static	dist. water	30(not available)	8	GC with flame ionisation	*Environ.Health Perspect*,57:193-197
102	2-(2-methoxyethoxy) ethanol	120.15	10.25	-1.18	3	1	0.000206	-3.69	none	isol. epidermis	abdomen	static	dist. water	30(not available)	8	GC with flame ionisation	*Environ.Health Perspect*,57:193-197
103	1-methoxylpropan-2-ol	90.12	10.16	-0.49	2	1	0.00125	-2.90	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation detection	*Environ.Health.Perspect*, 57:193-197
104	morphine	285.3	13.68	0.72	4	2	0.0000093	-5.03	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate phosphate buffer	37	52	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6: 825-832
105	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000581	-3.24	45% aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
106	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000598	-3.22	60 % aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
107	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000099	-4.00	90 % aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
108	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.0000632	-4.20	none	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
109	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00012	-3.92	60% aq. PEG 400	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
110	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000105	-3.98	75% aq. PEG 400	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
111	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00121	-2.92	30% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52:119-135
112	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.0004	-3.40	60% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52:119-135
113	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000016	-4.80	90% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52:119-135
114	2-naphthol	144.16	12.69	2.69	1	1	0.0279	-1.55	dist. water	isol. epidermis	abdomen	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
115	naproxene	230.3	11.42	3.1	2	1	0.00288	-2.54	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
116	nicorandil	211.18	14.40	0.43	3	1	0.000266	-3.58	water	full-thickness	breast	static	saline	37	32	HPLC	*J.Pharm.Sci.*, 7:231-236
117	nicotinic acid	123.11	13.23	0.69	2	1	0.000024	-4.62	water	isol. epidermis	abdomen / breast	static	isotonic PBS, NaCL	37	5	HPLC	*J.Pharm.Sci.*, 80:104-107
118	nicotine	162.3	11.25	1	2	0	0.0103	-1.99	0.05M phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	0.05M phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm.Sci.*, 11:59-68

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
119	nicotine	162.3	11.25	1	2	0	0.00331	-2.48	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
120	nimesulide	308.31	15.25	2.22	3	2	0.00101	-3	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37		HPLC	*J.Pharm.Science*, 92:3:656-664
121	3-nitrophenol	139.1	13.02	1.91	2	1	0.00564	-2.25	dist. water	isol. epidermis	abdomen	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
122	n-nitrosodiethanolamine	134.13	15.67	-1.28	4	2	0.0041	-2.39	isoprpyl myristate + sucrose (3H)	isol. epidermis	abdomen	static	PBS	32 (skin)	48	radiolabelled (14C)	*Food Chem.Toxicol.*,33:315-322
123	nizatidine	331.45	12.36	-0.43	5	2	0.000038	-4.43	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Science*, 92:3:656-664
124	nonane	128.3	7.51	4.76	0	0	0.000042	-4.38	JP-8	dermatom.0.56 mm	back	static	6% Volpo20 in PBS	32 (skin)	4	GC	*Toxicol.Sci.*, 55:247-255
125	n-octanol	130.23	9.45	2.81	1	1	0.061	-1.21	water	strarum corneum	abdomen	static	water	22 (not available)	48	radiolabelled (14C)	*Int.J.Pharm.*, 18:299-309
126	paraquat	257.16	10.45	-2.71	0	0	0.0000087	-5.06	water	full-thickness	abdomen	static	static	30	6	radiolabelled (14C)	*J.Investig.Dermatol.*, 96:921-925
127	4-n-pentylaniline	163.3	9.79	3.59	1	1	0.226	-0.65	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36		*I.J.Pharmac.* 129: 33-40
128	phenol	94.11	12.33	1.51	1	1	0.00822	-2.09	dist. water	isol. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
129	phenol	94.11	12.33	1.51	1	1	0.000149	-3.83	water	stratum corneum	abdomen	static	water	22 (not available)	10	UV spectrometry	*Int.J.Pharm.*,18:299-309
130	2-phenylethanol	122.2	11.38	1.57	1	1	0.031	-1.51	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36		*I.J.Pharmac.* 129: 33-40
131	4-phenylbutanol	150	10.80	2.55	1	1	0.0862	-1.06	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36		*I.J.Pharmac.* 129: 33-40
132	2-phenylphenol	170.21	12.24	3.28	1	1	0.0266	-1.58	60% aq. ethanol	isol. epidermis	dorsal / flank	static	saline (0.9% NaCL), 0.01% sodium azide & 3% BSA	32	8	radiolabelled (14C)	*Regul.Toxicol.Pharmacol.*, 35:198-208
133	2-phenylphenol	170.21	12.24	3.28	1	1	0.00159	-2.80	60% aq. ethanol	full-thickness	abdomen	static	Dulbecco's MEM, HEPES: Ham F-12, glutamx-I, BSA, L-glutamine, hydrocortisone & gentamycin	32	8	radiolabelled (14C)	*Regul.Toxicol.Pharmacol.*, 35:198-208
134	2-phenylphenol	170.21	12.24	3.28	1	1	0.0183	-1.74	60% aq. ethanol	isol. epidermis	abdomen	static	saline (0.9% NaCL), 0.01% sodium azide & 3% BSA	32	8	radiolabelled (14C)	*Regul.Toxicol.Pharmacol.*, 35:198-208
135	pregnenolone	316.5	10.36	3.89	2	1	0.0015	-2.82	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52:63-70
136	progesterone	314.5	10.05	3.67	2	0	0.0015	-2.82	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52:63-70
137	progesterone	314.5	10.05	3.67	2	0	0.03	-1.52	not available	isol. epidermis	various	static	not available	37 (not available)	not available	radiolabelled (14C)	J.Pharm. Sci., 84:1144-1146
138	propoxur	209.25	10.31	1.9	2	1	0.0000288	-4.54	aq. methanol	full-thickness	abdomen	static	RPMI, L-glutamine, gentamycin & 10% foetal calf serum	37	22	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.*, 123:144-150
139	propoxur	209.25	10.31	1.9	2	1	0.0407	-1.39	aq. methanol	full-thickness	abdomen	static	RPMI, L-glutamine, gentamycin & 10% foetal calf serum	37	22	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.*, 123:144-150
140	propoxur	209.25	10.31	1.9	2	1	0.000885	-3.05	60% aq. ethanol	full-thickness	abdomen	static	culture medium & 10% fetal bovine serum	32	24	radiolabelled (14C)	*Toxicol.Sci.*, 58:15-22
141	ranitidine	314.1	11.41	0.29	5	2	0.0000887	-4.05	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Science*, 92:3:656-664
142	resorcinol	110.11	15.18	1.03	2	2	0.00024	-3.62	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
143	salicylic acid	138.1	14.39	2.24	2	2	2.19	0.34	90% aq. propylene glycol	dermatom. 0.6 mm	abdomen	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215:51-56
144	salicylic acid	138.1	14.39	2.24	2	2	0.0131	-1.89	phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
145	salicylic acid	138.1	14.39	2.24	2	2	0.00133	-2.88	not available	dermatom. 0.5 mm	breast	static	MEM, Ham's F-12, sodium bicarbonate, HEPES & gentamycin sulphate	37	12	radiolabelled (14C)	*J.Toxicol.: Cutaneous Ocul.Toxicol.*, 12:129-138
146	salicylic acid	138.1	14.39	2.24	2	2	0.01194	-1.92	0.1M phosphate buffer (pH2)	full-thickness	breast	static	Tris.HCL buffer sol.	25	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
147	salicylic acid	138.1	14.39	2.24	2	2	0.00074	-3.13	0.1M phosphate buffer (pH4)	full-thickness	breast	static	Tris.HCL buffer sol.	25	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418
148	salicylic acid	138.1	14.39	2.24	2	2	0.00133	-2.88	not available	dermat. 0.5 mm	abdomen	static	MEM, Ham's F-12, sodium bicarbonate, HEPES & gentamycin sulphate	37	12	radiolabelled (14C)	*J.Toxicol.: Cutaneous Ocul.Toxicol.*, 12:129-138
149	salicylic acid	138.1	14.39	2.24	2	2	0.0138	-1.86	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*, 170: 129-133
150	squaric acid	114.06	20.47	-0.44	4	2	0.0000075	-5.12	acetone	dermatom.	thigh	static	buffer	not available	48	UV spectroscopy	*Arch.Dermatol.Res.*, 280:57-60
151	sufentanil	386.6	10.47	3.62	3	0	0.012	-1.92	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate phosphate buffer	37	8.5	GLC with nitrogen selective detector	*Pharm.Res*, 6:825-832
152	terbinafine	291.4	9.33	5.81	1	0	0.001	-3.00	propylene glycol	dermatomed 0.6 mm	abdomen	static	PBS ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*,215:51-56
153	testosterone	288.4	10.66	3.27	2	1	0.00012	-3.92	ethanol	full-thickness	abdomen	static	culture medium & 10% BSA	32	22	radiolabelled (14C)	*J.Control.Release*, 36: 327-335
154	testosterone	288.4	10.66	3.27	2	1	0.005012	-2.30	0.05M phosphate buffer 20% ethanol	dermatom. 0.41 mm	abdomen / breast	static	0.05M phosphate buffer	32 (skin)	28	radiolabelled (14C)	*Eur.J.Pharm.Sci.*, 11:59-68
155	testosterone	288.4	10.66	3.27	2	1	0.0004	-3.40	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled	*J.Invest.Derm.*,49:5S2
156	thymol	150.2	10.81	3.52	1	1	0.0528	-1.28	dist. water	isol. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
157	triclosan	289.55	10.02	2.47	2	1	0.000034	-4.47	methanol and adhesive Durotak 387-2051	isol. epidermis	breast and abdomen	static	ethanol & PBS	37	12	HPLC	*Int.J.Pharm.*,235:229-236
158	3,4 xylenol	202.55	11.54	2.61	1	1	0.036	-1.44	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
159	water	18.02	26.68	-1.38	1	1	0.000754	-3.12	saline	full-thickness	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
160	water	18.02	26.68	-1.38	1	1	0.000689	-3.16	saline	isol. epidermis	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
161	water	18.02	26.68	-1.38	1	1	0.00091	-3.04	saline	isol. epidermis	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
162	water	18.02	26.68	-1.38	1	1	0.00118	-2.93	saline	dermatomed 0.13 mm	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
163	water	18.02	26.68	-1.38	1	1	0.000707	-3.15	saline	dermatomed 0.13 mm	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
164	water	18.02	26.68	-1.38	1	1	0.00171	-2.77	none	dermatomed skin	abdomen	static	0.9% SALINE	30 (not available)	not available	radiolabelled (3H)	*J.Pharm.Pharmacol.*, 36:261-262
165	methyl paraben	152.15	12.5	2	2	1	0.00000589	-5.23	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci.*, 96, No. 4, 2007

Group A13

Type of skin: human Site: all types All temperatures Time Any analytical tool Vehicle: any Receptor fluid Buffered solutions

Cell type: static / flow through

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	nicotine	162.3	11.25	1	2	0	0.0103	-1.99	0.05M phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	0.05M phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
2	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000581	-3.24	45% aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
3	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000598	-3.22	60 % aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
4	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000099	-4.00	90 % aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
5	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.0000632	-4.20	none	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
6	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00012	-3.92	60% aq. PEG 400	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
7	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000105	-3.98	75% aq. PEG 400	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
8	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00121	-2.92	30% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52:119-135
9	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.0004	-3.40	60% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52:119-135
10	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000016	-4.80	90% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52:119-135
11	mannitol	182.17	18.63	-3.01	6	6	0.000011	-4.96	dist. water	full-thickness	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
12	mannitol	182.17	18.63	-3.01	6	6	0.000011	-4.96	dist. water	isol. epidermis	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
13	mannitol	182.17	18.63	-3.01	6	6	0.000025	-4.60	dist. water	isol. epidermis	abdomen	flow-through	0.9% physiological saline	32	48	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
14	mannitol	182.17	18.63	-3.01	6	6	0.000025	-4.60	dist. water	dermat.0.13 mm	abdomen	flow-through	0.9% physiological saline	not available	not available	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
15	water	18.02	26.68	-1.38	1	1	0.000754	-3.12	saline	full-thickness	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
16	water	18.02	26.68	-1.38	1	1	0.000689	-3.16	saline	isol. epidermis	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
17	water	18.02	26.68	-1.38	1	1	0.00091	-3.04	saline	isol. epidermis	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
18	water	18.02	26.68	-1.38	1	1	0.00118	-2.93	saline	dermatomed 0.13 mm	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
19	water	18.02	26.68	-1.38	1	1	0.000707	-3.15	saline	dermatomed 0.13 mm	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
20	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000136	-5.87	40% propylene glycol	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
21	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000306	-5.51	propylene glycol & dodecylazacycloheptan-2-one	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
22	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.0000026	-5.59	propylene glycol & 5% dimethylsulphoxide	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
23	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000338	-5.47	propylene glycol & sodium lauryl sulphate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
24	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000282	-5.55	propylene glycol & dodecyl-L-pyroglutamate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
25	testosterone	288.4	10.66	3.27	2	1	0.005012	-2.30	0.05M phosphate buffer 20% ethanol	dermatom. 0.41 mm	abdomen / breast	static	0.05M phosphate buffer	32 (skin)	28	radiolabelled (14C)	*Eur.J.Pharm.Sci.*, 11:59-68
26	water	18.02	26.68	-1.38	1	1	0.00171	-2.77	none	dermatomed skin	abdomen	static	0.9% SALINE	30 (not available)	not available	radiolabelled (3H)	*J.Pharm.Pharmacol.*, 36:261-262
27	dibutyl squarate	226.27	10.58	2.45	4	0	0.00002	-4.70	acetone	dermatomed skin	thigh	static	buffer	not given	48	UV spectroscopy	*Arch.Dermatol.Res.*, 280:57-60
28	diethyl squarate	170.16	11.50	4.07	4	0	0.00012	-3.92	acetone	dermatomed skin	thigh	static	buffer	not available	48	UV spectroscopy	*Arch.Dermatol.Res.*, 280:57-60
29	squaric acid	114.06	20.47	-0.44	4	2	0.0000075	-5.12	acetone	dermatom.	thigh	static	buffer	not available	48	UV spectroscopy	*Arch.Dermatol.Res.*,280:57-60
30	morphine	285.3	13.68	0.72	4	2	0.0000093	-5.03	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate phosphate buffer	37	52	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6: 825-832
31	sufentanil	386.6	10.47	3.62	3	0	0.012	-1.92	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate phosphate buffer	37	8.5	GLC with nitrogen selective detector	*Pharm.Res*,6:825-832
32	codeine	299.4	12.09	1.28	4	1	0.000049	-4.31	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	24	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6:825-832
33	fentanyl	336.5	10.30	3.89	2	0	0.0056	-2.25	physiological buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	9	GCL with Nitrogen selective detector	*Pharm.Res.*, 6: 825-832

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
34	hydromorphone	285.34	10.96	1.6	4	1	0.000015	-4.82	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	56	GLC with nitrogen selective detector	*Pharm.Res.*, 6: 825-832
35	meperidine	247.4	9.82	3.03	2	0	0.0037	-2.43	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	8	GLC with nitrogen selective detector	*Pharm.Res.* 6:825-832
36	naltrexone (NTX)	341	13.75	1.39	5	2	0.0095	-2.02	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
37	NTX-3-acetate (ACE-NTX)	383	12.96	1.47	5	1	0.0077	-2.11	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
38	NTX-3-propionate (PROP-NTX)	397	12.06	1.96	5	1	0.0025	-2.6	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
39	NTX-3-butyrate (BUT-NTX)	411	11.88	2.45	5	1	0.0013	-2.89	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
40	NTX-3-valerate (VAL-NTX)	425	11.72	2.45	5	1	0.0007	-3.15	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
41	NTX-3-hexanoate (HEX-NTX)	439	11.57	2.94	5	1	0.0012	-2.92	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
42	NTX-3 heptanoate (HEP-NTX)	453	11.44	3.92	5	1	0.0009	-3.05	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
43	etodolac	287.26	10.86	3.93	3	2	0.00746	-2.13	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
44	ketoprofen	254.29	11.75	3.12	2	1	0.00062	-3.21	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
45	nimesulide	308.31	15.25	2.22	3	2	0.00101	-3	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
46	nizatidine	331.45	12.36	-0.43	5	2	0.000038	-4.43	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
47	ranitidine	314.1	11.41	0.29	5	2	0.0000887	-4.05	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
48	etorphine	411.55	11.76	3.02	5	2	0.0036	-2.44	HCL & isotonic TRIS buffer	full-thickness	abdominal	static	isotonic TRIS buffer	37	24	radiolabelled (3H)	*Pharm.Res.*, 9: 963-965
49	bisoprolol	325.5	10.01	1.84	5	2	0.00027	-3.57	Sorensen's phosphate buffer (pH7.4)	dermatom. 1.2 mm	abdominal	flow-through	normal saline	32	72	HPLC	*Int.J.Pharm.*, 173:141-148
50	celiprolol	379.5	11.51	1.93	5	3	0.00059	-3.23	Sorensen's phosphate buffer (pH7.4)	dermatom. 1.2 mm	abdominal	flow-through	normal saline	32	72	HPLC	*Int.J.Pharm.*, 173:141-148
51	benzoic acid	122.1	11.94	1.87	1	1	0.025	-1.60	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.* 170:129-133
52	benzoic acid	122.1	11.94	1.87	1	1	0.00133	-2.88	deionised water	dermatomed 0.6 mm	not available	flow-through	PBS	37	48	radiolabelled (14C)	*J.Pharm.Sci.*, 85:249-252
53	borax	201.22	not calc.	not calc.	0	0	0.00017	-3.77	water	dermatom.0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
54	boric acid	61.83	44.06	-0.22	3	3	0.00029	-3.54	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
55	boric acid	61.83	44.06	-0.22	3	3	0.0000014	-5.85	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
56	boric acid	61.83	44.06	-0.22	3	3	0.00012	-3.92	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
57	boric acid	61.83	44.06	-0.22	3	3	0.0005	-3.30	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
58	butyl paraben	194.23	11.45	3.47	2	1	0.0277	-1.56	deionised water	epidermis	abdomen	static	PBS	23	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
59	butyl paraben	194.23	11.45	3.47	2	1	0.056	-1.25	deionised water	epidermis	abdomen	static	PBS	30	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
60	butyl paraben	194.23	11.45	3.47	2	1	0.0996	-1	deionised water	epidermis	abdomen	static	PBS	37	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
61	butyl paraben	194.23	11.45	3.47	2	1	0.275	-0.56	deionised water	epidermis	abdomen	static	PBS	45	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
62	caffeine	194.2	32.83	0.16	4	0	0.000258	-3.59	water	isol. epidermis	upper leg	static	PBS	37	24	HPLC	*Int.J.Pharm.*, 182:41-47
63	dichlofenac	296.16	11.13	4.02	2	2	0.001	-3.00	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.* , 170:129-133
64	disodium octaborate tetrahydrate	412.52	28	not calc.	28	12	8.00E-05	-4.10	water	dermat.0.5 mm	thigh	flow-through	PBS	32 (skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
65	glyphosate	169.10	12.73	-4.47	3	4	0.000459	-3.34	water	dermatom. 1mm	not available	flow-through	PBS	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,34:731-735
66	ibuprofen	206.3	10.21	3.79	1	1	0.0363	-1.44	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
67	malathion	330.36	10.61	2.29	2	0	0.203	-0.69	aq. ethanol	dermat. 1mm	not available	flow-through	PBS	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,34:731-735
68	methyl nicotinate	137.14	11.80	0.64	2	0	0.00389	-2.41	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
69	methyl paraben	152.15	12.5	2	2	1	0.00418	-2.38	deionised water	epidermis	abdomen	static	PBS	23	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
70	methyl paraben	152.15	12.5	2	2	1	0.00943	-2.03	deionised water	epidermis	abdomen	static	PBS	30	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
71	methyl paraben	152.15	12.5	2	2	1	0.0213	-1.67	deionised water	epidermis	abdomen	static	PBS	37	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
72	methyl paraben	152.15	12.5	2	2	1	0.032	-1.49	deionised water	epidermis	abdomen	static	PBS	45	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
73	naproxene	230.3	11.42	3.1	2	1	0.00288	-2.54	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
74	nicotine	162.3	11.25	1	2	0	0.00331	-2.48	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
75	n-nitrosodiethanolamine	134.13	15.67	-1.28	4	2	0.0041	-2.39	isoprpyl myristate +sucrose (3H)	isol. epidermis	abdomen	static	PBS	32 (skin)	48	radiolabelled (14C)	*Food Chem.Toxicol.*,33:315-322
76	salicylic acid	138.1	14.39	2.24	2	2	0.0138	-1.86	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*, 170:129-133
77	testosterone	288.4	10.66	3.27	2	1	0.0002399	-3.62	deionised	dermatom. 0.6 mm	not available	flow-through	PBS	27	48	radiolabelled (14C)	*J.Pharm.Sci.*, 85:249-252
78	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00000477	-5.32	ethanol	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
79	doxycycline HCL	444.44	16.55	-1.36	9	6	0.000211	-3.68	2:1 ethanol : M840	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
80	doxycycline HCL	444.44	16.55	-1.36	9	6	0.000266	-3.58	1:1 ethanol : M840	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
81	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00253	-2.6	2:1 ethanol : M840	epidermis	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
82	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00252	-2.6	1:1 ethanol : M840	epidermis	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
83	griseofulvin	352.77	10.44	1.92	6	0	0.0013	-2.89	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
84	griseofulvin	352.77	10.44	1.92	6	0	0.00194	-2.71	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
85	salicylic acid	138.1	14.39	2.24	2	2	0.0131	-1.89	phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
86	coumarin	146.15	11.91	1.51	1	0	0.0091	-2.04	phosphate buffer (pH 7.4)	full-thickness	abdomen	static	phosphate buffer (pH 7.4)	37	48	radiolabelled (14C)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
87	coumarin	146.15	11.91	1.51	1	0	0.0125	-1.90	phosphate buffer (pH 7.4)	full-thickness	scalp	static	phosphate buffer (pH 7.4)	37	48	radiolabelled (14C)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
88	dimethylformamide	73.1	10.63	-0.93	1	0	0.0096	-2.02	none	full-thickness	abdomen	flow-through	physiological solution	37	4	gas chromatography	*Occup.Hyg.*, 1:191-198
89	2-ethoxyethanol	90.12	10.33	-0.42	2	1	0.000882	-3.05	none	full-thickness	abdomen	flow-through	physiological solution	37	4	gas chromatography	*Occup.Hygiene*,1:191-198

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
90	caffeine	194.2	32.83	0.16	4	0	0.00072	-3.14	petrolatum	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol*., 115:1-11
91	caffeine	194.2	32.83	0.16	4	0	0.00062	-7.39	petrolatum	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol*., 115:1-11
92	caffeine	194.2	32.83	0.16	4	0	0.00021	-3.68	ethylene glycol	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol*., 115:1-11
93	caffeine	194.2	32.83	0.16	4	0	0.00051	-3.29	water gel	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol*., 115:1-11
94	ethanol	46.07	10.92	-0.14	1	1	0.000317	-3.50	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol*., 96: 921-925
95	mannitol	182.17	18.63	-3.01	6	6	0.000061	-4.21	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol*., 96:921-925
96	methotrexate	454.45	15.05	-1.28	10	5	0.000318	-3.50	50% aq. propylene glycol	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm*., 25:65-75
97	methotrexate	454.45	15.05	-1.28	10	5	0.000113	-3.95	0.03M HCL % aq. propylene glycol (pH 1.98)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm*., 25:65-75
98	methotrexate	454.45	15.05	-1.28	10	5	0.000562	-3.25	0.001M KOH, 50% aq. propylene glycol (pH 4.12)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm*., 25:65-75
99	methotrexate	454.45	15.05	-1.28	10	5	0.00113	-2.95	0.01M KOH, 50% aq. propylene glycol (pH 5.29)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm*., 25:65-75
100	methotrexate	454.45	15.05	-1.28	10	5	0.00052	-3.28	0.05 M KOH, 50% aq. propylene glycol (pH 6.34)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm*., 25:65-75
101	nicorandil	211.18	14.40	0.43	3	1	0.000266	-3.58	water	full-thickness	breast	static	saline	37	32	HPLC	*J.Pharm.Sci*., 7:231-236
102	testosterone	288.4	10.66	3.27	2	1	0.00028	-3.55	petrolatum	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol*.,115:1-11
103	testosterone	288.4	10.66	3.27	2	1	0.00018	-3.74	ethylene glycol	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol*.,115:1-11
104	testosterone	288.4	10.66	3.27	2	1	0.00671	-2.17	water gel	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol*.,115:1-11
105	atenolol	266.3	12.49	-0.03	4	3	0.00005	-4.30	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm*., 194: 249-259
106	flufenamic acid	281.2	10.96	4.88	5	2	0.0005209	-3.28	wool alcohols ointment	sc 0.012 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel*., 75:283-295
107	flufenamic acid	281.2	10.96	4.88	5	2	0.0005407	-3.27	wool alcohols ointment	sc 0.012 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel*., 75:283-295
108	flufenamic acid	281.2	10.96	4.88	5	2	0.0003889	-3.41	wool alcohols ointment	sc 0.012 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel*., 75:283-295
109	flufenamic acid	281.2	10.96	4.88	5	2	0.0005499	-3.26	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel*., 75:283-295
110	flufenamic acid	281.2	10.96	4.88	5	2	0.0005107	-3.29	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel*., 75:283-295
111	flufenamic acid	281.2	10.96	4.88	5	2	0.0003798	-3.42	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel*., 75:283-295
112	flufenamic acid	281.2	10.96	4.88	5	2	0.0000397	-4.40	wool alcohols ointment	full-thickness	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel*., 75:283-295
113	flufenamic acid	281.2	10.96	4.88	5	2	0.0000929	-4.03	wool alcohols ointment	full-thickness	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel*., 75:283-295
114	flufenamic acid	281.2	10.96	4.88	5	2	0.0000371	-4.43	wool alcohols ointment	full-thickness	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel*., 75:283-295
116	metoprolol	267.4	10.39	1.69	4	2	0.00083	-3.08	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm*., 194: 249-259
117	oxprenolol	265.4	10.52	1.83	4	2	0.00154	-2.81	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm*., 194: 249-259
118	propranolol	295.3	11.13	2.6	3	2	0.00178	-2.75	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm*., 194: 249-259

No	Name	MW	SP (cal/cm^3)$^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
119	paraquat	257.16	10.45	-2.71	0	0	0.0000087	-5.06	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol*., 96:921-925
120	methyl paraben	152.15	12.5	2	2	1	0.00000589	-5.23	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci*., 96,No.4, 2007
121	butyl paraben	194.23	11.45	3.47	2	1	0.000029	-4.54	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci*., 96,No.4, 2007

Group A14

Type of skin: human Site: all types All temperatures Time Any analytical tool Vehicle: any Receptor fluid Water

Cell type: static / flow through

No	Name	MW	SP (cal/cm^3)$^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	thymol	150.2	10.81	3.52	1	1	0.0528	-1.28	dist. water	isol. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol*., 29:677-683
2	4-bromophenol	173.01	11.48	2.4	1	1	0.03612	-1.44	dist. water	isol. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol*., 29:677-683
3	2-butoxyethanol	118.18	9.88	0.57	2	1	0.000214	-3.67	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect*., 57:193-197
4	2-(2-butoxyethoxy) ethanol	162.23	9.74	0.29	3	1	0.0000357	-4.45	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect*., 57:193-197
5	chloroxylenol	156.6	11.20	3.25	1	1	0.05904	-1.23	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol*.,29:677-683
6	2-cresol (o-cresol)	108.1	11.89	2.06	1	1	0.01572	-1.80	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol*.,29:677-683
7	3-cresol (m-cresol)	108.14	11.89	2.06	1	1	0.01524	-1.82	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol*.,29:677-683
8	4-cresol (p-cresol)	108.1	11.89	2.06	1	1	0.01752	-1.76	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol*.,29:677-683
9	2-ethoxyethanol	90.12	10.33	-0.42	2	1	0.000842	-3.07	none	full-thickness	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect*., 57:193-197
10	2-(2-ethoxyethoxy) ethanol	134.18	10.04	-0.69	3	1	0.000132	-3.88	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect*., 57:193-197
11	2-ethoxyethyl acetate	132.16	9.22	0.59	2	0	0.000807	-3.09	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect*., 57:193-197
12	2-methoxyethanol	76.1	10.67	-0.91	2	1	0.00289	-2.54	none	isol. epidermis	abdomen	static	dist. water	30(not available)	8	GC with flame ionisation	*Environ.Health Perspect*,57:193-197
13	2-(2-methoxyethoxy) ethanol	120.15	10.25	-1.18	3	1	0.000206	-3.69	none	isol. epidermis	abdomen	static	dist. water	30(not available)	8	GC with flame ionisation	*Environ.Health Perspect*,57:193-197
14	1-methoxylpropan-2-ol	90.12	10.16	-0.49	2	1	0.00125	-2.90	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation detection	*Environ.Health.Perspect*, 57:193-197
15	2-naphthol	144.16	12.69	2.69	1	1	0.0279	-1.55	dist. water	isol. epidermis	abdomen	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol*., 29:677-683
16	3-nitrophenol	139.1	13.02	1.91	2	1	0.00564	-2.25	dist. water	isol. epidermis	abdomen	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol*.,29:677-683
17	phenol	94.11	12.33	1.51	1	1	0.00822	-2.09	dist. water	isol. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol*., 29:677-683
18	resorcinol	110.11	15.18	1.03	2	2	0.00024	-3.62	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol*.,29:677-683
19	3,4 xylenol	202.55	11.54	2.61	1	1	0.036	-1.44	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol*.,29:677-683
20	methanol	32.04	11.68	-0.84	1	1	0.0016	-2.80	water	stratum corneum membrane	abdomen	static	WATER	22 (not available)	48	radiolabelled	*Int.J.Pharm*., 18: 299-309
21	n-octanol	130.23	9.45	2.81	1	1	0.061	-1.21	water	strarum corneum	abdomen	static	water	22 (not available)	48	radiolabelled (14C)	*Int.J.Pharm*., 18:299-309

No	Name	MW	SP (cal/cm^3)$^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
22	phenol	94.11	12.33	1.51	1	1	0.000149	-3.83	water	stratum corneum	abdomen	static	water	22 (not available)	10	UV spectrometry	*Int.J.Pharm.*,18:299-309
23	methyl paraben	152.15	12.5	2	2	1	0.00000589	-5.23	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci.*, 96, No. 4, 2007
24	butyl paraben	194.23	11.45	3.47	2	1	0.000029	-4.54	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci.*, 96, No. 4, 2007

Group A15

Type of skin: human Site: all types All temperatures Time Any analytical tool Vehicle: any Receptor fluid Buffered solutions

Cell type: static / flow through

No	Name	MW	SP (cal/cm^3)$^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	nicotine	162.3	11.25	1	2	0	0.0103	-1.99	0.05M phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	0.05M phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
2	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000581	-3.24	45% aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
3	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000598	-3.22	60 % aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
4	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000099	-4.00	90 % aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
5	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.0000632	-4.20	none	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
6	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00012	-3.92	60% aq. PEG 400	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
7	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000105	-3.98	75% aq. PEG 400	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
8	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00121	-2.92	30% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52:119-135
9	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.0004	-3.40	60% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52:119-135
10	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000016	-4.80	90% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52:119-135
11	mannitol	182.17	18.63	-3.01	6	6	0.000011	-4.96	dist. water	full-thickness	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
12	mannitol	182.17	18.63	-3.01	6	6	0.000011	-4.96	dist. water	isol. epidermis	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
13	mannitol	182.17	18.63	-3.01	6	6	0.000025	-4.60	dist. water	isol. epidermis	abdomen	flow-through	0.9% physiological saline	32	48	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
14	mannitol	182.17	18.63	-3.01	6	6	0.000025	-4.60	dist. water	dermat.0.13 mm	abdomen	flow-through	0.9% physiological saline	not available	not available	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
15	water	18.02	26.68	-1.38	1	1	0.000754	-3.12	saline	full-thickness	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
16	water	18.02	26.68	-1.38	1	1	0.000689	-3.16	saline	isol. epidermis	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
17	water	18.02	26.68	-1.38	1	1	0.00091	-3.04	saline	isol. epidermis	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
18	water	18.02	26.68	-1.38	1	1	0.00118	-2.93	saline	dermatomed 0.13 mm	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
19	water	18.02	26.68	-1.38	1	1	0.000707	-3.15	saline	dermatomed 0.13 mm	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
20	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000136	-5.87	40% propylene glycol	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
21	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000306	-5.51	propylene glycol & dodecylazacycloheptan-2-one	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
22	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.0000026	-5.59	propylene glycol & 5% dimethylsulphoxide	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
23	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000338	-5.47	propylene glycol & sodium lauryl sulphate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
24	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000282	-5.55	propylene glycol & dodecyl-L-pyroglutamate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
25	testosterone	288.4	10.66	3.27	2	1	0.005012	-2.30	0.05M phosphate buffer 20% ethanol	dermatom. 0.41 mm	abdomen / breast	static	0.05M phosphate buffer	32 (skin)	28	radiolabelled (14C)	*Eur.J.Pharm.Sci.*, 11:59-68
26	water	18.02	26.68	-1.38	1	1	0.00171	-2.77	none	dermatomed skin	abdomen	static	0.9% SALINE	30 (not available)	not available	radiolabelled (3H)	*J.Pharm.Pharmacol.*, 36:261-262
27	dibutyl squarate	226.27	10.58	2.45	4	0	0.00002	-4.70	acetone	dermatomed skin	thigh	static	buffer	not given	48	UV spectroscopy	*Arch.Dermatol.Res.*, 280:57-60
28	diethyl squarate	170.16	11.50	4.07	4	0	0.00012	-3.92	acetone	dermatomed skin	thigh	static	buffer	not available	48	UV spectroscopy	*Arch.Dermatol.Res.*, 280:57-60
29	squaric acid	114.06	20.47	-0.44	4	2	0.0000075	-5.12	acetone	dermatom.	thigh	static	buffer	not available	48	UV spectroscopy	*Arch.Dermatol.Res.*,280:57-60
30	morphine	285.3	13.68	0.72	4	2	0.0000093	-5.03	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate phosphate buffer	37	52	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6: 825-832
31	sufentanil	386.6	10.47	3.62	3	0	0.012	-1.92	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate phosphate buffer	37	8.5	GLC with nitrogen selective detector	*Pharm.Res*,6:825-832
32	codeine	299.4	12.09	1.28	4	1	0.000049	-4.31	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	24	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6:825-832
33	fentanyl	336.5	10.30	3.89	2	0	0.0056	-2.25	physiological buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	9	GCL with Nitrogen selective detector	*Pharm.Res.*, 6: 825-832
34	hydromorphone	285.34	10.96	1.6	4	1	0.000015	-4.82	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	56	GLC with nitrogen selective detector	*Pharm.Res.*, 6: 825-832
35	meperidine	247.4	9.82	3.03	2	0	0.0037	-2.43	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	8	GLC with nitrogen selective detector	*Pharm.Res.* 6:825-832
36	naltrexone (NTX)	341	13.75	1.39	5	2	0.0095	-2.02	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
37	NTX-3-acetate (ACE-NTX)	383	12.96	1.47	5	1	0.0077	-2.11	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
38	NTX-3-propionate (PROP-NTX)	397	12.06	1.96	5	1	0.0025	-2.6	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
39	NTX-3-butyrate (BUT-NTX)	411	11.88	2.45	5	1	0.0013	-2.89	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
40	NTX-3-valerate (VAL-NTX)	425	11.72	2.45	5	1	0.0007	-3.15	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
41	NTX-3-hexanoate (HEX-NTX)	439	11.57	2.94	5	1	0.0012	-2.92	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
42	NTX-3 heptanoate (HEP-NTX)	453	11.44	3.92	5	1	0.0009	-3.05	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
43	etodolac	287.26	10.86	3.93	3	2	0.00746	-2.13	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Science*, 92:3:656-664
44	ketoprofen	254.29	11.75	3.12	2	1	0.00062	-3.21	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Science*, 92:3:656-664
45	nimesulide	308.31	15.25	2.22	3	2	0.00101	-3	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Science*, 92:3:656-664
46	nizatidine	331.45	12.36	-0.43	5	2	0.000038	-4.43	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Science*, 92:3:656-664
47	ranitidine	314.1	11.41	0.29	5	2	0.0000887	-4.05	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Science*, 92:3:656-664
48	etorphine	411.55	11.76	3.02	5	2	0.0036	-2.44	HCL & isotonic TRIS buffer	full-thickness	abdominal	static	isotonic TRIS buffer	37	24	radiolabelled (3H)	*Pharm.Res.*, 9: 963-965
49	bisoprolol	325.5	10.01	1.84	5	2	0.00027	-3.57	Sorensen's phosphate buffer (pH7.4)	dermatom. 1.2 mm	abdominal	flow-through	normal saline	32	72	HPLC	*Int.J.Pharm.*, 173:141-148

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
50	celiprolol	379.5	11.51	1.93	5	3	0.00059	-3.23	Sorensen's phosphate buffer (pH7.4)	dermatom. 1.2 mm	abdominal	flow-through	normal saline	32	72	HPLC	*Int.J.Pharm.*, 173:141-148
51	benzoic acid	122.1	11.94	1.87	1	1	0.025	-1.60	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.* 170:129-133
52	benzoic acid	122.1	11.94	1.87	1	1	0.00133	-2.88	deionised water	dermatomed 0.6 mm	not available	flow-through	PBS	37	48	radiolabelled (14C)	*J.Pharm.Sci.*, 85:249-252
53	borax	201.22	not calc.	not calc.	0	0	0.00017	-3.77	water	dermatom.0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
54	boric acid	61.83	44.06	-0.22	3	3	0.00029	-3.54	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
55	boric acid	61.83	44.06	-0.22	3	3	0.0000014	-5.85	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
56	boric acid	61.83	44.06	-0.22	3	3	0.00012	-3.92	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
57	boric acid	61.83	44.06	-0.22	3	3	0.0005	-3.30	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
58	butyl paraben	194.23	11.45	3.47	2	1	0.0277	-1.56	deionised water	epidermis	abdomen	static	PBS	23	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
59	butyl paraben	194.23	11.45	3.47	2	1	0.056	-1.25	deionised water	epidermis	abdomen	static	PBS	30	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
60	butyl paraben	194.23	11.45	3.47	2	1	0.0996	-1	deionised water	epidermis	abdomen	static	PBS	37	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
61	butyl paraben	194.23	11.45	3.47	2	1	0.275	-0.56	deionised water	epidermis	abdomen	static	PBS	45	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
62	caffeine	194.2	32.83	0.16	4	0	0.000258	-3.59	water	isol. epidermis	upper leg	static	PBS	37	24	HPLC	*Int.J.Pharm.*, 182:41-47
63	dichlofenac	296.16	11.13	4.02	2	2	0.001	-3.00	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.* , 170:129-133
64	disodium octaborate tetrahydrate	412.52	28	not calc.	28	12	8.00E-05	-4.10	water	dermat.0.5 mm	thigh	flow-through	PBS	32 (skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
65	glyphosate	169.10	12.73	-4.47	3	4	0.000459	-3.34	water	dermatom. 1mm	not available	flow-through	PBS	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,34:731-735
66	ibuprofen	206.3	10.21	3.79	1	1	0.0363	-1.44	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
67	malathion	330.36	10.61	2.29	2	0	0.203	-0.69	aq. ethanol	dermat. 1mm	not available	flow-through	PBS	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,34:731-735
68	methyl nicotinate	137.14	11.80	0.64	2	0	0.00389	-2.41	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
69	methyl paraben	152.15	12.5	2	2	1	0.00418	-2.38	deionised water	epidermis	abdomen	static	PBS	23	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
70	methyl paraben	152.15	12.5	2	2	1	0.00943	-2.03	deionised water	epidermis	abdomen	static	PBS	30	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
71	methyl paraben	152.15	12.5	2	2	1	0.0213	-1.67	deionised water	epidermis	abdomen	static	PBS	37	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
72	methyl paraben	152.15	12.5	2	2	1	0.032	-1.49	deionised water	epidermis	abdomen	static	PBS	45	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
73	methyl paraben	152.15	12.5	2	2	1	not calc.	not calc.	not available	not available	not available	not available	not available	not available	not available	not available	
74	naproxene	230.3	11.42	3.1	2	1	0.00288	-2.54	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
75	nicotine	162.3	11.25	1	2	0	0.00331	-2.48	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
76	n-nitrosodiethanolamine	134.13	15.67	-1.28	4	2	0.0041	-2.39	isoprpyl myristate +sucrose (3H)	isol. epidermis	abdomen	static	PBS	32 (skin)	48	radiolabelled (14C)	*Food Chem.Toxicol.*,33:315-322
77	salicylic acid	138.1	14.39	2.24	2	2	0.0138	-1.86	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*, 170:129-133

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78	testosterone	288.4	10.66	3.27	2	1	0.0002399	-3.62	deionised	dermatom. 0.6 mm	not available	flow-through	PBS	27	48	radiolabelled (14C)	*J.Pharm.Sci*., 85:249-252
79	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00000477	-5.32	ethanol	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
80	doxycycline HCL	444.44	16.55	-1.36	9	6	0.000211	-3.68	2:1 ethanol : M840	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
81	doxycycline HCL	444.44	16.55	-1.36	9	6	0.000266	-3.58	1:1 ethanol : M840	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
82	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00253	-2.6	2:1 ethanol : M840	epidermis	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
83	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00252	-2.6	1:1 ethanol : M840	epidermis	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
84	griseofulvin	352.77	10.44	1.92	6	0	0.0013	-2.89	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
85	griseofulvin	352.77	10.44	1.92	6	0	0.00194	-2.71	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
86	salicylic acid	138.1	14.39	2.24	2	2	0.0131	-1.89	phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm.Sci*., 11:59-68
87	coumarin	146.15	11.91	1.51	1	0	0.0091	-2.04	phosphate buffer (pH 7.4)	full-thickness	abdomen	static	phosphate buffer (pH 7.4)	37	48	radiolabelled (14C)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
88	coumarin	146.15	11.91	1.51	1	0	0.0125	-1.90	phosphate buffer (pH 7.4)	full-thickness	scalp	static	phosphate buffer (pH 7.4)	37	48	radiolabelled (14C)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
89	dimethylformamide	73.1	10.63	-0.93	1	0	0.0096	-2.02	none	full-thickness	abdomen	flow-through	physiological solution	37	4	gas chromatography	*Occup.Hyg*., 1:191-198
90	2-ethoxyethanol	90.12	10.33	-0.42	2	1	0.000882	-3.05	none	full-thickness	abdomen	flow-through	physiological solution	37	4	gas chromatography	*Occup.Hygiene*,1:191-198
91	caffeine	194.2	32.83	0.16	4	0	0.00072	-3.14	petrolatum	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol*., 115:1-11
92	caffeine	194.2	32.83	0.16	4	0	0.00062	-7.39	petrolatum	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol*., 115:1-11
93	caffeine	194.2	32.83	0.16	4	0	0.00021	-3.68	ethylene glycol	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol*., 115:1-11
94	caffeine	194.2	32.83	0.16	4	0	0.00051	-3.29	water gel	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol*., 115:1-11
95	ethanol	46.07	10.92	-0.14	1	1	0.000317	-3.50	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol*., 96: 921-925
96	mannitol	182.17	18.63	-3.01	6	6	0.000061	-4.21	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol*., 96:921-925
97	methotrexate	454.45	15.05	-1.28	10	5	0.000318	-3.50	50% aq. propylene glycol	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm*., 25:65-75
98	methotrexate	454.45	15.05	-1.28	10	5	0.000113	-3.95	0.03M HCL % aq. propylene glycol (pH 1.98)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm*., 25:65-75
99	methotrexate	454.45	15.05	-1.28	10	5	0.000562	-3.25	0.001M KOH, 50% aq. propylene glycol (pH 4.12)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm*., 25:65-75
100	methotrexate	454.45	15.05	-1.28	10	5	0.00113	-2.95	0.01M KOH, 50% aq. propylene glycol (pH 5.29)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm*., 25:65-75
101	methotrexate	454.45	15.05	-1.28	10	5	0.00052	-3.28	0.05 M KOH, 50% aq. propylene glycol (pH 6.34)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm*., 25:65-75
102	nicorandil	211.18	14.40	0.43	3	1	0.000266	-3.58	water	full-thickness	breast	static	saline	37	32	HPLC	*J.Pharm.Sci*., 7:231-236
103	testosterone	288.4	10.66	3.27	2	1	0.00028	-3.55	petrolatum	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol*.,115:1-11
104	testosterone	288.4	10.66	3.27	2	1	0.00018	-3.74	ethylene glycol	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol*.,115:1-11
105	testosterone	288.4	10.66	3.27	2	1	0.00671	-2.17	water gel	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol*.,115:1-11

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
106	atenolol	266.3	12.49	-0.03	4	3	0.00005	-4.30	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
107	flufenamic acid	281.2	10.96	4.88	5	2	0.0005209	-3.28	wool alcohols ointment	sc 0.012 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
108	flufenamic acid	281.2	10.96	4.88	5	2	0.0005407	-3.27	wool alcohols ointment	sc 0.012 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
109	flufenamic acid	281.2	10.96	4.88	5	2	0.0003889	-3.41	wool alcohols ointment	sc 0.012 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
110	flufenamic acid	281.2	10.96	4.88	5	2	0.0005499	-3.26	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
111	flufenamic acid	281.2	10.96	4.88	5	2	0.0005107	-3.29	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
112	flufenamic acid	281.2	10.96	4.88	5	2	0.0003798	-3.42	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
113	flufenamic acid	281.2	10.96	4.88	5	2	0.0000397	-4.40	wool alcohols ointment	full-thickness	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
114	flufenamic acid	281.2	10.96	4.88	5	2	0.0000929	-4.03	wool alcohols ointment	full-thickness	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
115	flufenamic acid	281.2	10.96	4.88	5	2	0.0000371	-4.43	wool alcohols ointment	full-thickness	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
116	metoprolol	267.4	10.39	1.69	4	2	0.00083	-3.08	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
117	oxprenolol	265.4	10.52	1.83	4	2	0.00154	-2.81	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
118	propranolol	295.3	11.13	2.6	3	2	0.00178	-2.75	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
119	paraquat	257.16	10.45	-2.71	0	0	0.0000087	-5.06	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol.*, 96:921-925
120	methyl paraben	152.15	12.5	2	2	1	0.00000589	-5.23	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci.*, 96,No.4, 2007
121	butyl paraben	194.23	11.45	3.47	2	1	0.000029	-4.54	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci.*, 96,No.4, 2007
122	thymol	150.2	10.81	3.52	1	1	0.0528	-1.28	dist. water	isol. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
123	4-bromophenol	173.01	11.48	2.4	1	1	0.03612	-1.44	dist. water	isol. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
124	2-butoxyethanol	118.18	9.88	0.57	2	1	0.000214	-3.67	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
125	2-(2-butoxyethoxy) ethanol	162.23	9.74	0.29	3	1	0.0000357	-4.45	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
126	chloroxylenol	156.6	11.20	3.25	1	1	0.05904	-1.23	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
127	2-cresol (o-cresol)	108.1	11.89	2.06	1	1	0.01572	-1.80	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
128	3-cresol (m-cresol)	108.14	11.89	2.06	1	1	0.01524	-1.82	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
129	4-cresol (p-cresol)	108.1	11.89	2.06	1	1	0.01752	-1.76	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
130	2-ethoxyethanol	90.12	10.33	-0.42	2	1	0.000842	-3.07	none	full-thickness	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
131	2-(2-ethoxyethoxy) ethanol	134.18	10.04	-0.69	3	1	0.000132	-3.88	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
132	2-ethoxyethyl acetate	132.16	9.22	0.59	2	0	0.000807	-3.09	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
133	2-methoxyethanol	76.1	10.67	-0.91	2	1	0.00289	-2.54	none	isol. epidermis	abdomen	static	dist. water	30(not available)	8	GC with flame ionisation	*Environ.Health Perspect*,57:193-197

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
134	2-(2-methoxyethoxy) ethanol	120.15	10.25	-1.18	3	1	0.000206	-3.69	none	isol. epidermis	abdomen	static	dist. water	30(not available)	8	GC with flame ionisation	*Environ.Health Perspect*,57:193-197
135	1-methoxylpropan-2-ol	90.12	10.16	-0.49	2	1	0.00125	-2.90	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation detection	*Environ.Health.Perspect*, 57:193-197
136	2-naphthol	144.16	12.69	2.69	1	1	0.0279	-1.55	dist. water	isol. epidermis	abdomen	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
137	3-nitrophenol	139.1	13.02	1.91	2	1	0.00564	-2.25	dist. water	isol. epidermis	abdomen	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
138	phenol	94.11	12.33	1.51	1	1	0.00822	-2.09	dist. water	isol. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
139	resorcinol	110.11	15.18	1.03	2	2	0.00024	-3.62	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
140	3,4 xylenol	202.55	11.54	2.61	1	1	0.036	-1.44	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
141	methanol	32.04	11.68	-0.84	1	1	0.0016	-2.80	water	stratum corneum membrane	abdomen	static	WATER	22 (not available)	48	radiolabelled	*Int.J.Pharm.*, 18: 299-309
142	n-octanol	130.23	9.45	2.81	1	1	0.061	-1.21	water	strarum corneum	abdomen	static	water	22 (not available)	48	radiolabelled (14C)	*Int.J.Pharm.*, 18:299-309
143	phenol	94.11	12.33	1.51	1	1	0.000149	-3.83	water	stratum corneum	abdomen	static	water	22 (not available)	10	UV spectrometry	*Int.J.Pharm.*,18:299-309
144	methyl paraben	152.15	12.5	2	2	1	0.00000589	-5.23	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci.*, 96, No. 4, 2007
145	butyl paraben	194.23	11.45	3.47	2	1	0.000029	-4.54	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci.*, 96, No. 4, 2007

Group A16

Type of skin: human Site: all types All temperatures Time Any analytical tool Vehicle: any Receptor fluid any

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	5-fluorouracil	130.01	13.46	-0.81	3	2	0.0000166	-4.78	0.002% aq. sodium azide solution	dermatomed 0.42 mm	abdomen	flow-through	0.002% aq. sodium azide solution	31	24	radiolabelled (3H)	*J.Investig.Pharmacol.*, 94:235-240
2	water	18.02	26.68	-1.38	1	1	0.0013	-2.89	none	dermatomed 0.42 mm	abdomen	flow-through	0.002% sodium azide solution	31 (skin)	6	radiolabelled (3H)	*J.Invest.Dermatol.*, 94:235-240
3	nicotine	162.3	11.25	1	2	0	0.0103	-1.99	0.05M phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	0.05M phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
4	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000581	-3.24	45% aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
5	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000598	-3.22	60 % aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
6	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000099	-4.00	90 % aq. propylene glycol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
7	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.0000632	-4.20	none	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
8	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00012	-3.92	60% aq. PEG 400	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
9	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000105	-3.98	75% aq. PEG 400	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Contr.Release*, 67:211-221
10	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00121	-2.92	30% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52:119-135
11	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.0004	-3.40	60% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52:119-135
12	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.000016	-4.80	90% aq. ethanol	full-thickness	not available	static	0.1 M pH 7.4 PBS	37	36	HPLC	*J.Toxicol.Environ.Health*, 52:119-135

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
13	benzene	78.12	9.19	1.99	0	0	0.111	-0.95	water	isol. epidermis	abdomen	static	0.1% NaCL solution	31 (skin)	4	HPLC	*J.Invest.Dermatol.*,85: 522-526
14	benzene	78.12	9.19	1.99	0	0	0.00094	-3.03	hexodecane	isol. epidermis	abdomen	static	0.1% NaCL solution	31 (skin)	0	HPLC	*J.Invest.Dermatol.*,85: 522-526
15	benzene	78.12	9.19	1.99	0	0	0.1665	-0.78	isoctane	isol. epidermis	abdomen	static	0.1% NaCL solution	31 (skin)	0	HPLC	*J.Invest.Dermatol.*,85: 522-526
16	benzene	78.12	9.19	1.99	0	0	0.0024	-2.62	isoctane	isol. epidermis	abdomen	static	0.1% NaCL solution	31 (skin)	0	HPLC	*J.Invest.Dermatol.*,85: 522-526
17	benzene	78.12	9.19	1.99	0	0	0.00011	-3.96	isoctane	isol. epidermis	abdomen	static	0.1% NaCL solution	31 (skin)	0	HPLC	*J.Invest.Dermatol.*,85: 522-526
18	mannitol	182.17	18.63	-3.01	6	6	0.000011	-4.96	dist. water	full-thickness	abdomen	static	0.9% physiological saline		not available	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
19	mannitol	182.17	18.63	-3.01	6	6	0.000011	-4.96	dist. water	isol. epidermis	abdomen	static	0.9% physiological saline		not available	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
20	mannitol	182.17	18.63	-3.01	6	6	0.000025	-4.60	dist. water	isol. epidermis	abdomen	flow-through	0.9% physiological saline	32	48	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
21	mannitol	182.17	18.63	-3.01	6	6	0.000025	-4.60	dist. water	dermat.0.13 mm	abdomen	flow-through	0.9% physiological saline		not available	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
22	water	18.02	26.68	-1.38	1	1	0.000754	-3.12	saline	full-thickness	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
23	water	18.02	26.68	-1.38	1	1	0.000689	-3.16	saline	isol. epidermis	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
24	water	18.02	26.68	-1.38	1	1	0.00091	-3.04	saline	isol. epidermis	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
25	water	18.02	26.68	-1.38	1	1	0.00118	-2.93	saline	dermatomed 0.13 mm	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
26	water	18.02	26.68	-1.38	1	1	0.000707	-3.15	saline	dermatomed 0.13 mm	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
27	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000136	-5.87	40% propylene glycol	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
28	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000306	-5.51	propylene glycol & dodecylazacycloheptan-2-one	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
29	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.0000026	-5.59	propylene glycol & 5% dimethylsulphoxide	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
30	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000338	-5.47	propylene glycol & sodium lauryl sulphate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
31	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000282	-5.55	propylene glycol & dodecyl-L-pyroglutamate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472
32	testosterone	288.4	10.66	3.27	2	1	0.005012	-2.30	0.05M phosphate buffer 20% ethanol	dermatom. 0.41 mm	abdomen / breast	static	0.05M phosphate buffer	32 (skin)	28	radiolabelled (14C)	*Eur.J.Pharm.Sci.*, 11:59-68
33	water	18.02	26.68	-1.38	1	1	0.00171	-2.77	none	dermatomed skin	abdomen	static	0.9% SALINE	30 (not available)	not available	radiolabelled (3H)	*J.Pharm.Pharmacol.*, 36:261-262
34	androstedione	288.42	10.03	2.75	2	0	0.00124	-2.91	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
35	ethinyl estradiol	296.4	12.04	4	2	1	0.0000374	-4.43	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
36	prednisone	358.44	12.71	1.46	5	2	0.0000246	-4.61	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
37	prednisolone	360.44	12.96	1.49	5	3	0.0000235	-4.63	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
38	betamethasone	392.45	12.37	2.02	6	3	0.000002	-5.70	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
39	b-estradiol	272.4	11.90	3.94	2	2	0.01	-2.00	5% oleic acid, in 75% ethanol	dermatomed 0.5 mm	abdomen	static	5% oleic acid, in 75% ethanol	32	60	radiolabelled (3H)	*Pharm.Res.*, 10:1745-1750
40	chlorpyrifos	350.59	10.10	4.66	1	0	0.00025	-3.60	commercial solution containing xylene & 111-TCE	full-thickness	breast	flow-through	50% aq. ethanol	32 (skin)	24	gas chromatography	*Hum.Exp.Toxicol*,19:104-107

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
41	DEHP	390.57	9.39	8.39	2	0	0.0000057	-5.24	none	isol. epidermis	abdomen	static	50% aq. ethanol	30 (not available)	72	radiolabelled (14C)	*Environ.Health Perspect.*, 74:223-227
42	DEP	222.24	10.51	2.65	2	0	0.0000114	-4.94	none	isol. epidermis	abdomen	static	50% aq. ethanol	30 (not available)	30	radiolabelled (14C)	*Environ.Health Perspect.*, 74:223-227
43	dibutylphthalate	278.35	10.86	5.11	2	0	0.0000023	-5.64	none	isol. epidermis	abdomen	static	50% aq. ethanol	30 (not available)	30	radiolabelled (14C)	*Environ.Health Perspect.*, 74:223-227
44	lindane	290.83	8.54	4.26	0	0	0.0000059	-5.23	acetone	dermat. 0.23 mm	breast / abdomen	static	50% aq. ethanol	32 (skin)	6	gas chromatography	*Hum.Exp.Toxicol.*, 16: 652-657
45	lindane	290.83	8.54	4.26	0	0	0.0000059	-5.23	acetone	dermat. 0.23 mm	breast / abdomen	static	50% aq. ethanol	32 (skin)	24	gas chromatography	*Hum.Exp.Toxicol.*, 16: 652-657
46	chlorpyrifos	350.59	10.10	4.66	1	0	0.00011	-3.96	ethanol	full-thickness	breast	flow-through	50% aq. ethanol	32(skin)	24	gas chromatography	*Hum.Exp.Toxicol*,19:104-107
47	nonane	128.3	7.51	4.76	0	0	0.000042	-4.38	JP-8	dermatom.0.56 mm	back	static	6% Volpo20 in PBS	32 (skin)	4	GC	*Toxicol.Sci.*, 55:247-255
48	b-estradiol	272.4	11.90	3.94	2	2	0.001	-3.00	75%ethanol	dermatomed 0.5 mm	abdomen	static	75% ethanol	32	60	radiolabelled (3H)	*Pharm.Res.*, 10:1745-1750
49	aldosterone	360.45	12.31	1.63	4	2	3.00E-06	-5.52	water	isol. epidermis	not given	static	aq. penecillin / streptomycin	26 (not available)	not available	radiolabelled	*J.Invest.Dermatol.*, 52-63-70
50	b-estradiol	272.4	11.90	3.94	2	2	0.0003	-3.52	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52: 63-70
51	estriol	288.4	12.95	2.81	3	3	0.00004	-4.40	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52: 63-70
52	estrone	270.4	11.55	3.43	2	1	0.0036	-2.44	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52: 63-70
53	hydrocortisone	362.5	12.75	1.61	5	3	0.000003	-5.52	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled	*J.Investig.Dermatol.*, 52: 63-70
54	pregnenolone	316.5	10.36	3.89	2	1	0.0015	-2.82	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52:63-70
55	progesterone	314.5	10.05	3.67	2	0	0.0015	-2.82	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52:63-70
56	testosterone	288.4	10.66	3.27	2	1	0.0004	-3.40	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled	*J.Invest.Derm.*,49:5S2
57	cortexolone	346.47	11.91	3.15	4	2	0.000075	-4.12	water	isol. epidermis	not available	static	aq. penicillin /streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52:63-70
58	corticosterone	346.5	11.91	1.99	4	2	0.00006	-4.22	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52:63-70
59	cortisone	360.5	12.1	1.81	5	2	0.00001	-5.00	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52:63-70
60	adenosine	267.24	15.97	-1.05	9	4	0.000133	-3.88	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32(skin)	24	UV / VS	*Eur.J.Pharm.Sci.*, 2006
61	cimetidine	252.34	12.86	0.4	6	3	0.000038	-4.42	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32 (skin)	24	radiolabelled	*Eur.J.Pharm.Sci.*, 2006
62	deoxyadenosine	251.24	15.49	-0.55	8	3	0.000129	-3.89	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32 (skin)	24	UV / VS	*Eur.J.Pharm.Sci.*, 2006
63	methiocarb	225.31	10.92	2.87	1	1	0.0011	-2.96	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*,48:697-701
64	pirimicarb	238.29	11.05	1.4	4	0	0.0027	-2.57	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*,48:697-701
65	prochloraz	376.7	10.69	4.13	3	0	0.0007	-3.15	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*,48:697-701
66	dibutyl squarate	226.27	10.58	2.45	4	0	0.00002	-4.70	acetone	dermatomed skin	thigh	static	buffer	not given	48	UV spectroscopy	*Arch.Dermatol.Res.*, 280:57-60
67	diethyl squarate	170.16	11.50	4.07	4	0	0.00012	-3.92	acetone	dermatomed skin	thigh	static	buffer	not available	48	UV spectroscopy	*Arch.Dermatol.Res.*, 280:57-60
68	squaric acid	114.06	20.47	-0.44	4	2	0.0000075	-5.12	acetone	dermatom.	thigh	static	buffer	not available	48	UV spectroscopy	*Arch.Dermatol.Res.*, 280:57-60

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69	5-fluorouracil	130.01	13.46	-0.81	3	2	0.000601	-3.22	aq. buffered solution	epidermis	abdomen	static	buffered saline solution pH 7.4 + plysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
70	morphine	285.3	13.68	0.72	4	2	0.0000093	-5.03	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate phosphate buffer	37	52	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6: 825-832
71	sufentanil	386.6	10.47	3.62	3	0	0.012	-1.92	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate phosphate buffer	37	8.5	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6:825-832
72	codeine	299.4	12.09	1.28	4	1	0.000049	-4.31	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	24	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6:825-832
73	fentanyl	336.5	10.30	3.89	2	0	0.0056	-2.25	physiological buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	9	GCL with Nitrogen selective detector	*Pharm.Res.*, 6: 825-832
74	hydromorphone	285.34	10.96	1.6	4	1	0.000015	-4.82	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	56	GLC with nitrogen selective detector	*Pharm.Res.*, 6: 825-832
75	meperidine	247.4	9.82	3.03	2	0	0.0037	-2.43	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	8	GLC with nitrogen selective detector	*Pharm.Res.* 6:825-832
76	testosterone	288.4	10.66	3.27	2	1	0.00012	-3.92	ethanol	full-thickness	abdomen	static	culture medium & 10% BSA	32	22	radiolabelled (14C)	J.Control.Release, 76: 327-335.
77	propoxur	209.25	10.31	1.9	2	1	0.000885	-3.05	60% aq ethanol	full-thickness	abdomen	static	culture medium & 10% fetal bovine serum	32	24	radiolabelled (14C)	*Toxicol.Sci.*, 58:15-22
78	thymol	150.2	10.81	3.52	1	1	0.0528	-1.28	dist. water	isol. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
79	4-bromophenol	173.01	11.48	2.4	1	1	0.03612	-1.44	dist. water	isol. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
80	2-butoxyethanol	118.18	9.88	0.57	2	1	0.000214	-3.67	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
81	2-(2-butoxyethoxy) ethanol	162.23	9.74	0.29	3	1	0.0000357	-4.45	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
82	chloroxylenol	156.6	11.20	3.25	1	1	0.05904	-1.23	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
83	2-cresol (o-cresol)	108.1	11.89	2.06	1	1	0.01572	-1.80	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
84	3-cresol (m-cresol)	108.14	11.89	2.06	1	1	0.01524	-1.82	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
85	4-cresol (p-cresol)	108.1	11.89	2.06	1	1	0.01752	-1.76	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
86	2-ethoxyethanol	90.12	10.33	-0.42	2	1	0.000842	-3.07	none	full-thickness	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
87	2-(2-ethoxyethoxy) ethanol	134.18	10.04	-0.69	3	1	0.000132	-3.88	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
88	2-ethoxyethyl acetate	132.16	9.22	0.59	2	0	0.000807	-3.09	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
89	2-methoxyethanol	76.1	10.67	-0.91	2	1	0.00289	-2.54	none	isol. epidermis	abdomen	static	dist. water	30(not available)	8	GC with flame ionisation	*Environ.Health Perspect*,57:193-197
90	2-(2-methoxyethoxy) ethanol	120.15	10.25	-1.18	3	1	0.000206	-3.69	none	isol. epidermis	abdomen	static	dist. water	30(not available)	8	GC with flame ionisation	*Environ.Health Perspect*,57:193-197
91	1-methoxylpropan-2-ol	90.12	10.16	-0.49	2	1	0.00125	-2.90	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation detection	*Environ.Health.Perspect*, 57:193-197
92	2-naphthol	144.16	12.69	2.69	1	1	0.0279	-1.55	dist. water	isol. epidermis	abdomen	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
93	3-nitrophenol	139.1	13.02	1.91	2	1	0.00564	-2.25	dist. water	isol. epidermis	abdomen	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
94	phenol	94.11	12.33	1.51	1	1	0.00822	-2.09	dist. water	isol. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
95	resorcinol	110.11	15.18	1.03	2	2	0.00024	-3.62	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
96	3,4 xylenol	202.55	11.54	2.61	1	1	0.036	-1.44	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683

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97	2-phenylphenol	170.21	12.24	3.28	1	1	0.00159	-2.80	60% aq. ethanol	full-thickness	abdomen	static	Dulbecco's MEM, HEPES: Ham F-12, glutamx-I, BSA, L-glutamine, hydrocortisone & gentamycin	32	8	radiolabelled (14C)	*Regul.Toxicol.Pharmacol.*, 35:198-208
98	hydroquinone	110.11	15.18	1.03	2	2	9.33E-06	-5.03	not available	isol. epidermis	abdomen	static	Dulbecco's PBS, antibiotics and fungicides	30	8	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016
99	testosterone	288.4	10.66	3.27	2	1	0.0000267	-4.57	ethanol	dermatom. 0.28 mm	breast	flow-through	Eagles MEM & 2% PEG (pH 7.4)	32 (not available)	24	radiolabelled (14C)	*Toxicology*, 168:63
100	1-methoxylpropan-2-ol	90.12	10.16	-0.49	2	1	0.00144	-2.84	water	dermatom. 0.5 mm	breast	flow-through	Eagles MEM & sodium carbonate & gentamycin	32	24	radiolabelled (14C)	*Int.Arch.Occup.Environ.Health*, 75:519-527
101	1-methoxylpropan-2-ol	90.12	10.16	-0.49	2	1	0.000065	-4.19	none	dermatom. 0.5 mm	breast	flow-through	Eagles MEM & sodium carbonate & gentamycin	32	24	radiolabelled (14C)	*Int.Arch.Occup.Environ.Health*, 75:519-527
102	1-methoxylpropan-2-ol	90.12	10.16	-0.49	2	1	0.00065	-3.19	none	dermatom. 0.5 mm	breast	flow-through	Eagles MEM & sodium carbonate & gentamycin	32	24	radiolabelled (14C)	*Int.Arch.Occup.Environ.Health*, 75:519-527
103	parathion	291.26	10.76	3.73	1	0	0.000189	-3.72	none	dermatom. 0.5 mm	back	flow-through	Eagles-MEM-BSS & gentamycin	37	96	radiolabelled	*Toxicol.Appl.Pharmacol.*, 168:149-152
104	triclosan	289.55	10.02	2.47	2	1	0.000034	-4.47	methanol and adhesive Durotak 387-2051	isol. epidermis	breast and abdomen	static	ethanol & PBS	37	12	HPLC	*Int.J.Pharm.*,235:229-236
105	DDT	354.49	9.45	6.79	0	0	0.00594	-2.23	acetone	dermatomed 0.5 mm	abdomen	flow-through	Hanks HEPES buffered medium, 4% BSA & gentamycin	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 1225-1232
106	bisphenol A diglycidyl ether (BADGE)	340.8	10.38	3.84	4	0	4.80E-07	-6.32	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, BSA & gentamycin	32(skin)	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
107	o-cresyl glycidyl ether (oCGE)	164.2	10.38	2.16	2	0	9.30E-05	-4.03	acetone	dermatommed	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*,30:469-483
108	dodecyl glycidyl ether (C12GE)	242.2	8.41	5.01	2	0	0.00000331	-5.48	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
109	epikote YX4000	354.4	11.00	5.19	4	0	0.000000047	-7.33	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
110	1,6-hexanediol diglycidyl ether (HDDGE)	230.2	9.36	0.84	4	0	0.000136	-3.87	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32(skin)	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
111	2,4 dimethylamine	266.13	9.52	0.84	3	2	0.000945	-3.02	commercial formulation clean crop	dermatom.0.3 mm	abdomen	flow-through	HBSS, HEPES, buffer BSA & gentamycin sulphate	37	48	radiolabelled (14C)	*Toxicol.Vitro*,11:251-262
112	2,4 dimethylamine	266.13	9.52	0.84	3	2	0.00081	-3.09	commercial formulation Wilbur Ellis	dermatom.0.3 mm	abdomen	flow-through	HBSS, HEPES, buffer BSA & gentamycin sulphate	37	48	radiolabelled (14C)	*Toxicol.Vitro*,11:251-262
113	coumarin	146.15	11.91	1.51	1	0	0.000376	-3.42	ethanol	full-thickness	breast	flow-through	HEPES buffered HBSS & 0.5% gentamycin	32 (skin)	72	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.* 145:34-42
114	coumarin	146.15	11.91	1.51	1	0	0.000719	-3.14	ethanol	full-thickness	breast	flow-through	HEPES buffered HBSS & 0.5% gentamycin	32 (skin)	72	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.* 145:34-42
115	cannabinol	310.46	10.9	7.23	2	1	0.00015	-3.82	propylene glycol : water (7:3) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol.*, 56: 291-297
116	cannabidiol	314.46	11.11	8.01	2	2	0.00024	-3.62	propylene glycol : water (7:3) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol.*, 56: 291-297
117	Δ-tetrahydrocannabinol (THC)	314.46	9.75	7.6	2	1	0.000028	-4.55	propylene glycol : water : ethanol (9:1:1) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol.*, 56: 291-297
118	benzyl nicotinate	213.24	11.55	2.35	2	0	0.016	-1.80	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*, 80:54-56
119	benzyl nicotinate	213.24	11.55	2.35	2	0	2.04 E-05	-4.69	none	isol. epidermis		static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*, 80:54-56
120	butyl nicotinate	179.22	10.57	2.11	2	0	0.0166	-1.78	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37 (not available)	5	HPLC	*J.Pharm.Sci.*, 80:54-56
121	butyl nicotinate	179.22	10.57	2.11	2	0	0.000079	-4.10	none	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37 (not available)	5	HPLC	*J.Pharm.Sci.*, 80:54-56
122	ethyl nicotinate	151.17	11.06	1.13	2	2	0.00608	-2.22	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37(not available)	5	HPLC	*J.Pharm.Sci.*, 80:54-56
123	ethyl nicotinate	151.17	11.06	1.13	2	2	0.0066	-2.18	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37(not available)	5	HPLC	*J.Pharm.Sci.*, 80:54-56
124	ethyl nicotinate	151.17	11.06	1.13	2	2	0.000216	-3.65	none	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37(not available)	5	HPLC	*J.Pharm.Sci.*, 80:54-56

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
125	n-hexyl nicotinate	207.27	10.49	3.1	2	0	0.0179	-1.75	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*,80:54-56
126	n-hexyl nicotinate	207.27	10.49	3.1	2	0	1.22E-05	-4.91	none	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*,80:54-56
127	methyl nicotinate	137.14	11.80	0.64	2	0	0.00309	-2.51	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*,80:54-56
128	methyl nicotinate	137.14	11.80	0.64	2	0	0.0034	-2.47	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*,80:54-56
129	nicotinic acid	123.11	13.23	0.69	2	1	0.000024	-4.62	water	isol. epidermis	abdomen / breast	static	isotonic PBS, NaCL	37	5	HPLC	*J.Pharm.Sci.*, 80:104-107
130	naltrexone (NTX)	341	13.75	1.39	5	2	0.0095	-2.02	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
131	NTX-3-acetate (ACE-NTX)	383	12.96	1.47	5	1	0.0077	-2.11	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
132	NTX-3-propionate (PROP-NTX)	397	12.06	1.96	5	1	0.0025	-2.60	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
133	NTX-3-butyrate (BUT-NTX)	411	11.88	2.45	5	1	0.0013	-2.89	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
134	NTX-3-valerate (VAL-NTX)	425	11.72	2.45	5	1	0.0007	-3.15	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
135	NTX-3-hexanoate (HEX-NTX)	439	11.57	2.94	5	1	0.0012	-2.92	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
136	NTX-3 heptanoate (HEP-NTX)	453	11.44	3.92	5	1	0.0009	-3.05	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
137	etodolac	287.26	10.86	3.93	3	2	0.00746	-2.13	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
138	ketoprofen	254.29	11.75	3.12	2	1	0.00062	-3.21	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
139	nimesulide	308.31	15.25	2.22	3	2	0.00101	-3.00	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
140	nizatidine	331.45	12.36	-0.43	5	2	0.000038	-4.43	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
141	ranitidine	314.1	11.41	0.29	5	2	0.0000887	-4.05	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
142	etorphine	411.55	11.76	3.02	5	2	0.0036	-2.44	HCL & isotonic TRIS buffer	full-thickness	abdominal	static	isotonic TRIS buffer	37	24	radiolabelled (3H)	*Pharm.Res.*, 9: 963-965
143	2-phenoxyethanol	138.17	11.49	1.1	2	1	0.001337	-2.87	methanol	dermat.0.33	breast / abdomen / leg	flow-through	MEM & penicillin / streptomycin +CO2	37	6	HPLC	*Food Chem.Toxicol.*,35:1009-1016
144	salicylic acid	138.1	14.39	2.24	2	2	0.00133	-2.88	not available	dermatom. 0.5 mm	breast	static	MEM, Ham's F-12, sodium bicarbonate, HEPES & gentamycin sulphate	37	12	radiolabelled (14C)	*J.Toxicol.: Cutaneous Ocul.Toxicol.*, 12:129-138
145	salicylic acid	138.1	14.39	2.24	2	2	0.00133	-2.88	not available	dermat. 0.5 mm	abdomen	static	MEM, Ham's F-12, sodium bicarbonate, HEPES & gentamycin sulphate	37	12	radiolabelled (14C)	*J.Toxicol.: Cutaneous Ocul.Toxicol.*, 12:129-138
146	2-ethoxyethanol	90.12	10.33	-0.42	2	1	0.000059	-4.23	methanol	dermat. 0.28 mm	breast	flow-through	MEM, sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl.Pharmacol.*, 180:74-82
147	2-ethoxyethanol	90.12	10.33	-0.42	2	1	0.000074	-4.13	methanol	dermat. 0.28 mm	breast	flow-through	MEM, sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl.Pharmacol.*, 180:74-82
148	bisoprolol	325.5	10.01	1.84	5	2	0.00027	-3.57	Sorensen's phosphate buffer (pH7.4)	dermatom. 1.2 mm	abdominal	flow-through	normal saline	32	72	HPLC	*Int.J.Pharm.*, 173:141-148
149	celiprolol	379.5	11.51	1.93	5	3	0.00059	-3.23	Sorensen's phosphate buffer (pH7.4)	dermatom. 1.2 mm	abdominal	flow-through	normal saline	32	72	HPLC	*Int.J.Pharm.*, 173:141-148
150	theophylline	180.17	14.05	-0.39	4	1	0.000432	-3.36	water	dermatomed 0.2 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*, 40:231-242
151	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.000025	-4.60	PEG 400	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*,40:231-242
152	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00032	-3.49	propylene glycol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40:231-242

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
153	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.000287	-3.54	1-propanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40:231-242
154	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00054	-3.27	ethanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40:231-242
155	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00295	-2.53	methanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*,40:231-242
156	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00417	-2.38	water	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*,40:231-242
157	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00478	-2.32	water	dermatom. 0.32 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*,40:231-242
158	aldosterone	360.45	12.31	1.63	4	2	5.80E-05	-4.24	not available	isol. epidermis	various	static	not available	26 (not available)	not available	radiolabelled	*J.Pharm.Sci.*, 84:1144-1146
159	b-estradiol	272.4	11.90	3.94	2	2	0.0041	-2.39	water	isol. epidermis	various	static	not available	37	not available	radiolabelled (3H)	*J.Pharm.Sci.*, 84:1144-1146
160	progesterone	314.5	10.05	3.67	2	0	0.03	-1.52	not available	isol. epidermis	various	static	not available	37 (not available)	not available	radiolabelled (14C)	J.Pharm. Sci., 84:1144-1146
161	benzoic acid	122.1	11.94	1.87	1	1	0.025	-1.60	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.* 170:129-133
162	benzoic acid	122.1	11.94	1.87	1	1	0.00133	-2.88	deionised water	dermatomed 0.6 mm	not available	flow-through	PBS	37	48	radiolabelled (14C)	*J.Pharm.Sci.*, 85:249-252
163	borax	201.22	not calc.	not calc.	0	0	0.00017	-3.77	water	dermatom.0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
164	boric acid	61.83	44.06	-0.22	3	3	0.00029	-3.54	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
165	boric acid	61.83	44.06	-0.22	3	3	0.0000014	-5.85	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
166	boric acid	61.83	44.06	-0.22	3	3	0.00012	-3.92	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
167	boric acid	61.83	44.06	-0.22	3	3	0.0005	-3.30	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
168	butyl paraben	194.23	11.45	3.47	2	1	0.0277	-1.56	deionised water	epidermis	abdomen	static	PBS	23	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
169	butyl paraben	194.23	11.45	3.47	2	1	0.056	-1.25	deionised water	epidermis	abdomen	static	PBS	30	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
170	butyl paraben	194.23	11.45	3.47	2	1	0.0996	-1.00	deionised water	epidermis	abdomen	static	PBS	37	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
171	butyl paraben	194.23	11.45	3.47	2	1	0.275	-0.56	deionised water	epidermis	abdomen	static	PBS	45	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
172	caffeine	194.2	32.83	0.16	4	0	0.000258	-3.59	water	isol. epidermis	upper leg	static	PBS	37	24	HPLC	*Int.J.Pharm.*, 182:41-47
173	dichlofenac	296.16	11.13	4.02	2	2	0.001	-3.00	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*, 170:129-133
174	disodium octaborate tetrahydrate	412.52	28		28	12	8.00E-05	-4.10	water	dermat.0.5 mm	thigh	flow-through	PBS	32 (skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
175	glyphosate	169.10	12.73	-4.47	3	4	0.000459	-3.34	water	dermatom. 1mm	not available	flow-through	PBS	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,34:731-735
176	ibuprofen	206.3	10.21	3.79	1	1	0.0363	-1.44	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
177	malathion	330.36	10.61	2.29	2	0	0.203	-0.69	aq. ethanol	dermat. 1mm	not available	flow-through	PBS	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,34:731-735
178	methyl nicotinate	137.14	11.80	0.64	2	0	0.00389	-2.41	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
179	methyl paraben	152.15	12.5	2	2	1	0.00418	-2.38	deionised water	epidermis	abdomen	static	PBS	23	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
180	methyl paraben	152.15	12.5	2	2	1	0.00943	-2.03	deionised water	epidermis	abdomen	static	PBS	30	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
181	methyl paraben	152.15	12.5	2	2	1	0.0213	-1.67	deionised water	epidermis	abdomen	static	PBS	37	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
182	methyl paraben	152.15	12.5	2	2	1	0.032	-1.49	deionised water	epidermis	abdomen	static	PBS	45	4	HPLC	*Eur.J.Pharm.Sci.*, 21:337-345
183	naproxene	230.3	11.42	3.1	2	1	0.00288	-2.54	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
184	nicotine	162.3	11.25	1	2	0	0.00331	-2.48	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
185	n-nitrosodiethanolamine	134.13	15.67	-1.28	4	2	0.0041	-2.39	isoprpyl myristate + sucrose (3H)	isol. epidermis	abdomen	static	PBS	32 (skin)	48	radiolabelled (14C)	*Food Chem.Toxicol.*,33:315-322
186	salicylic acid	138.1	14.39	2.24	2	2	0.0138	-1.86	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*, 170:129-133
187	testosterone	288.4	10.66	3.27	2	1	0.0002399	-3.62	deionised	dermatom. 0.6 mm	not available	flow-through	PBS	27	48	radiolabelled (14C)	*J.Pharm.Sci.*, 85:249-252
188	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00000477	-5.32	ethanol	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
189	doxycycline HCL	444.44	16.55	-1.36	9	6	0.000211	-3.68	2:1 ethanol : M840	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
190	doxycycline HCL	444.44	16.55	-1.36	9	6	0.000266	-3.58	1:1 ethanol : M840	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
191	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00253	-2.60	2:1 ethanol : M840	epidermis	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
192	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00252	-2.60	1:1 ethanol : M840	epidermis	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
193	clotrimazole	344.85	11.17	6.26	2	0	0.002	-2.70	propylene glycol	dermatom. 0.6 mm	abdomen	static	PBS ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*,215:51-56
194	hydrocortisone	362.5	12.75	1.61	5	3	0.0023	-2.64	propylene glycol	dermat. 0.6 mm	abdomen	static	PBS ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215:51-56
195	salicylic acid	138.1	14.39	2.24	2	2	2.19	0.34	90% aq. propylene glycol	dermatom. 0.6 mm	abdomen	static	PBS ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215:51-56
196	terbinafine	291.4	9.33	5.81	1	0	0.001	-3.00	propylene glycol	dermatomed 0.6 mm	abdomen	static	PBS ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*,215:51-56
197	ITF 296	238	12.91	1.61	3	0	0.00356	-2.45	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
198	isosorbide dinitrate (ISDN)	236.14	10.36	0.76	4	0	0.00449	-2.35	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
199	nicorandil	211.18	14.40	0.43	3	1	0.00005	-4.30	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
200	griseofulvin	352.77	10.44	1.92	6	0	0.0013	-2.89	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
201	griseofulvin	352.77	10.44	1.92	6	0	0.00194	-2.71	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
202	salicylic acid	138.1	14.39	2.24	2	2	0.0131	-1.89	phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
203	coumarin	146.15	11.91	1.51	1	0	0.0091	-2.04	phosphate buffer (pH 7.4)	full-thickness	abdomen	static	phosphate buffer (pH 7.4)	37	48	radiolabelled (14C)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
204	coumarin	146.15	11.91	1.51	1	0	0.0125	-1.90	phosphate buffer (pH 7.4)	full-thickness	scalp	static	phosphate buffer (pH 7.4)	37	48	radiolabelled (14C)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
205	linoleic acid	289.45	9.05	7.51	1	1	0.0000106	-4.97	ethanol	full-thickness	abdomen	static	phosphate buffer, pluronic F88 & BHT	37	95	radiolabelled (14C)	*J.Pharm.Pharmacol.*, 34:610-611
206	dimethylformamide	73.1	10.63	-0.93	1	0	0.0096	-2.02	none	full-thickness	abdomen	flow-through	physiological solution	37	4	gas chromatography	*Occup.Hyg.*, 1:191-198
207	2-ethoxyethanol	90.12	10.33	-0.42	2	1	0.000882	-3.05	none	full-thickness	abdomen	flow-through	physiological solution	37	4	gas chromatography	*Occup.Hygiene*,1:191-198
208	propoxur	209.25	10.31	1.9	2	1	0.0000288	-4.54	aq. methanol	full-thickness	abdomen	static	RPMI, L-glutamine, gentamycin & 10% foetal calf serum	37	22	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.*, 123:144-150

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
209	propoxur	209.25	10.31	1.9	2	1	0.0407	-1.39	aq. methanol	full-thickness	abdomen	static	RPMI, L-glutamine, gentamycin & 10% foetal calf serum	37	22	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.*, 123:144-150
210	caffeine	194.2	32.83	0.16	4	0	0.00072	-3.14	petrolatum	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol.*, 115:1-11
211	caffeine	194.2	32.83	0.16	4	0	0.00062	-7.39	petrolatum	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol.*, 115:1-11
212	caffeine	194.2	32.83	0.16	4	0	0.00021	-3.68	ethylene glycol	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol.*, 115:1-11
213	caffeine	194.2	32.83	0.16	4	0	0.00051	-3.29	water gel	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol.*, 115:1-11
214	ethanol	46.07	10.92	-0.14	1	1	0.000317	-3.50	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol.*, 96: 921-925
215	mannitol	182.17	18.63	-3.01	6	6	0.000061	-4.21	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol.*, 96:921-925
216	methotrexate	454.45	15.05	-1.28	10	5	0.000318	-3.50	50% aq. propylene glycol	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm.*, 25:65-75
217	methotrexate	454.45	15.05	-1.28	10	5	0.000113	-3.95	0.03M HCL % aq. propylene glycol (pH 1.98)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm.*, 25:65-75
218	methotrexate	454.45	15.05	-1.28	10	5	0.000562	-3.25	0.001M KOH, 50% aq. propylene glycol (pH 4.12)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm.*, 25:65-75
219	methotrexate	454.45	15.05	-1.28	10	5	0.00113	-2.95	0.01M KOH, 50% aq. propylene glycol (pH 5.29)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm.*, 25:65-75
220	methotrexate	454.45	15.05	-1.28	10	5	0.00052	-3.28	0.05 M KOH, 50% aq. propylene glycol (pH 6.34)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm.*, 25:65-75
221	nicorandil	211.18	14.40	0.43	3	1	0.000266	-3.58	water	full-thickness	breast	static	saline	37	32	HPLC	*J.Pharm.Sci.*, 7:231-236
222	testosterone	288.4	10.66	3.27	2	1	0.00028	-3.55	petrolatum	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115:1-11
223	testosterone	288.4	10.66	3.27	2	1	0.00018	-3.74	ethylene glycol	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115:1-11
224	testosterone	288.4	10.66	3.27	2	1	0.00671	-2.17	water gel	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115:1-11
225	2-phenylphenol	170.21	12.24	3.28	1	1	0.0266	-1.58	60% aq. ethanol	isol. epidermis	dorsal / flank	static	saline (0.9% NaCL), 0.01% sodium azide & 3% BSA	32	8	radiolabelled (14C)	*Regul.Toxicol.Pharmacol.*, 35:198-208
226	2-phenylphenol	170.21	12.24	3.28	1	1	0.0183	-1.74	60% aq. ethanol	isol. epidermis	abdomen	static	saline (0.9% NaCL), 0.01% sodium azide & 3% BSA	32	8	radiolabelled (14C)	*Regul.Toxicol.Pharmacol.*, 35:198-208
227	nikel	58.7	0	-0.57	0	0	0.00061	-3.21	synthetic sweat pH 6.5	full-thickness	abdomen	static	saline solution 0.9% NaCl	32(skin)	24	electrothermal spectrometry	*Toxicology Letters* 170 (2007), 49-56
228	aniline	93	10.83	1.08	1	1	6.10E-02	-1.21	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
229	4-n-butylaniline	149.24	9.51	3.1	1	1	0.411	-0.39	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
230	ethylaniline	121.2	9.73	2.11	1	1	0.288	-0.54	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
231	4-n-pentylaniline	163.3	9.79	3.59	1	1	0.226	-0.65	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
232	2-phenylethanol	122.2	11.38	1.57	1	1	0.031	-1.51	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
233	4-phenylbutanol	150	10.80	2.55	1	1	0.0862	-1.06	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
234	lidocaine	234.34	8.78	1.66	2	1	0.000344	-3.46	40% propylene glycol & HCL (pH4)	dermat. 0.15 mm	leg	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (14C)	*Int.J.Pharm.*, 71:167-173
235	lidocaine	234.34	8.78	1.66	2	1	0.000388	-3.41	40% propylene glycol & HCL (pH6)	dermat. 0.15 mm	leg	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (14C)	*Int.J.Pharm.*, 71:167-173
236	lidocaine	234.34	8.78	1.66	2	1	0.0106	-1.97	40% propylene glycol & HCL (pH10)	dermat. 0.15 mm	leg	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (14C)	*Int.J.Pharm.*, 71:167-173

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
237	methyl parathion	263.21	10.45	2.75	1	0	0.000013	-4.87	acetone	full-thickness	abdomen	static	saline, 4% BSA & gentamycin sulphate	32 (skin)	48	gas chromatography	*Occup.Environ.Med.*,54:524-525
238	methyl parathion	263.21	10.45	2.75	1	0	0.000038	-4.42	20% MPA, 75% xylene, 5% dispersing agents	full-thickness	abdomen	static	saline, 4%BSA & gentamycin sulphate	32(skin)	48	gas chromatography	*Occup.Environ.Med.*,54:524-525
239	hydrocortisone	362.5	12.75	1.61	5	3	0.000158	-3.80	Britton-Robinson 0.2M buffers & ethanol, pH1	full-thickness	abdomen	flow-through	solution of NaCl & sodium azide	37	28	HPLC	*J.Contr.Release*, 76:327-335
240	hydrocortisone	362.5	12.75	1.61	5	3	0.000075	-4.12	Britton-Robinson 0.2M buffers & ethanol, pH6	full-thickness	abdomen	flow-through	solution of NaCl & sodium azide	37	28	HPLC	*J.Contr.Release*, 76:327-335
241	hydrocortisone	362.5	12.75	1.61	5	3	0.000095	-4.02	Britton-Robinson 0.2M buffers & ethanol, pH10	full-thickness	abdomen	flow-through	solution of NaCl & sodium azide	37	28	HPLC	*J.Contr.Release*, 76:327-335
242	testosterone	288.4	10.66	3.27	2	1	0.012	-1.92	0.1M phosphate buffer pH1	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
243	testosterone	288.4	10.66	3.27	2	1	0.0117	-1.93	0.1M phosphate buffer pH2	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
244	testosterone	288.4	10.66	3.27	2	1	0.00912	-2.04	hydrochloric acid and potassium chloride pH2	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
245	testosterone	288.4	10.66	3.27	2	1	0.012	-1.92	0.1M phosphate buffer pH6	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
246	testosterone	288.4	10.66	3.27	2	1	0.04	-1.40	0.1M phosphate buffer pH12	full-thickness	abdomen	flow-through	solution of NaCL (0.9%) & sodium azide (0.005%)	37	28	HPLC	*J.Contr.Release*, 76: 327-335
247	atenolol	266.3	12.49	-0.03	4	3	0.00005	-4.30	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
248	flufenamic acid	281.2	10.96	4.88	5	2	0.0005209	-3.28	wool alcohols ointment	sc 0.012 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
249	flufenamic acid	281.2	10.96	4.88	5	2	0.0005407	-3.27	wool alcohols ointment	sc 0.012 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
250	flufenamic acid	281.2	10.96	4.88	5	2	0.0003889	-3.41	wool alcohols ointment	sc 0.012 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
251	flufenamic acid	281.2	10.96	4.88	5	2	0.0005499	-3.26	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
252	flufenamic acid	281.2	10.96	4.88	5	2	0.0005107	-3.29	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
253	flufenamic acid	281.2	10.96	4.88	5	2	0.0003798	-3.42	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
254	flufenamic acid	281.2	10.96	4.88	5	2	0.0000397	-4.40	wool alcohols ointment	full-thickness	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
255	flufenamic acid	281.2	10.96	4.88	5	2	0.0000929	-4.03	wool alcohols ointment	full-thickness	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
256	flufenamic acid	281.2	10.96	4.88	5	2	0.0000371	-4.43	wool alcohols ointment	full-thickness	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
257	metoprolol	267.4	10.39	1.69	4	2	0.00083	-3.08	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
258	oxprenolol	265.4	10.52	1.83	4	2	0.00154	-2.81	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
259	propranolol	295.3	11.13	2.6	3	2	0.00178	-2.75	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
260	paraquat	257.16	10.45	-2.71	0	0	0.0000087	-5.06	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol.*, 96:921-925
261	diazinon	304.35	14.98	3.86	2	1	0.0095	-2.02	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, trizma, glucose	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8:1219-1224
262	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00224	-2.65	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 7:141-148
263	salicylic acid	138.1	14.39	2.24	2	2	0.01194	-1.92	0.1M phosphate buffer (pH2)	full-thickness	breast	static	Tris.HCL buffer sol.	25	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418
264	salicylic acid	138.1	14.39	2.24	2	2	0.00074	-3.13	0.1M phosphate buffer (pH4)	full-thickness	breast	static	Tris.HCL buffer sol.	25	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
265	methanol	32.04	11.68	-0.84	1	1	0.0016	-2.80	water	stratum corneum membrane	abdomen	static	WATER	22 (not available)	48	radiolabelled	*Int.J.Pharm.*, 18: 299-309
266	n-octanol	130.23	9.45	2.81	1	1	0.061	-1.21	water	strarum corneum	abdomen	static	water	22 (not available)	48	radiolabelled (14C)	*Int.J.Pharm.,* 18:299-309
267	phenol	94.11	12.33	1.51	1	1	0.000149	-3.83	water	stratum corneum	abdomen	static	water	22 (not available)	10	UV spectrometry	*Int.J.Pharm.*,18:299-309
268	methyl paraben	152.15	12.5	2	2	1	0.00000589	-5.23	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci*., 96, No. 4, 2007
269	butyl paraben	194.23	11.45	3.47	2	1	0.000029	-4.54	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci*., 96, No. 4, 2007

Group A17

Type of skin: human Site: all types All temperatures Time Any analytical tool Vehicle: any Receptor fluid any

No duplicates

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	1,6-hexanediol diglycidyl ether (HDDGE)	230.2	9.36	0.84	4	0	0.000136	-3.87	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32(skin)	24	radiolabelled (14C)	*Xenobiotica,* 30:469-483
2	1-methoxylpropan-2-ol	90.12	10.16	-0.49	2	1	0.00065	-3.19	none	dermatom. 0.5 mm	breast	flow-through	Eagles MEM & sodium carbonate & gentamycin	32	24	radiolabelled (14C)	*Int.Arch.Occup.Environ.Health,* 75:519-527
3	2-(2-butoxyethoxy) ethanol	162.23	9.74	0.29	3	1	0.0000357	-4.45	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect*., 57:193-197
4	2-(2-ethoxyethoxy) ethanol	134.18	10.04	-0.69	3	1	0.000132	-3.88	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect*., 57:193-197
5	2-(2-methoxyethoxy) ethanol	120.15	10.25	-1.18	3	1	0.000206	-3.69	none	isol. epidermis	abdomen	static	dist. water	30(not available)	8	GC with flame ionisation	*Environ.Health Perspect*., 57:193-197
6	2,4 dimethylamine	266.13	9.52	0.84	3	2	0.000945	-3.02	commercial formulation clean crop	dermatom.0.3 mm	abdomen	flow-through	HBSS, HEPES, buffer BSA & gentamycin sulphate	37	48	radiolabelled (14C)	*Toxicol. Vitro,*11:251-262
7	2-butoxyethanol	118.18	9.88	0.57	2	1	0.000214	-3.67	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect*., 57:193-197
8	2-cresol (o-cresol)	108.1	11.89	2.06	1	1	0.01572	-1.80	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
9	2-ethoxyethanol	90.12	10.33	-0.42	2	1	0.000842	-3.07	none	full-thickness	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect*., 57:193-197
10	2-ethoxyethyl acetate	132.16	9.22	0.59	2	0	0.000807	-3.09	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect*., 57:193-197
11	2-methoxyethanol	76.01	10.67	-0.91	2	1	0.00289	-2.54	none	isol. epidermis	abdomen	static	dist. water	30(not available)	8	GC with flame ionisation	*Environ.Health Perspect,*57:193-197
12	2-naphthol	144.16	12.69	2.69	1	1	0.0279	-1.55	dist. water	isol. epidermis	abdomen	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.,* 29:677-683
13	2-phenoxyethanol	138.17	11.49	1.1	2	1	0.001337	-2.87	methanol	dermat.0.33	breast / abdomen / leg	flow-through	MEM & penicillin / streptomycin +CO2	37	6	HPLC	*Food Chem.Toxicol.*,35:1009-1016
14	2-phenylethanol	122.2	11.38	1.57	1	1	0.031	-1.51	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
15	2-phenylphenol	170.21	12.24	3.28	1	1	0.0183	-1.74	60% aq. ethanol	isol. epidermis	abdomen	static	saline (0.9% NaCL), 0.01% sodium azide & 3% BSA	32	8	radiolabelled (14C)	*Regul.Toxicol.Pharmacol.*, 35:198-208
16	3,4 xylenol	202.55	11.54	2.61	1	1	0.036	-1.44	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
17	3-cresol (m-cresol)	108.14	11.89	2.06	1	1	0.01524	-1.82	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
18	3-nitrophenol	139.1	13.02	1.91	2	1	0.00564	-2.25	dist. water	isol. epidermis	abdomen	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
19	4-bromophenol	173.01	11.48	2.4	1	1	0.03612	-1.44	dist. water	isol. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol*., 29:677-683
20	4-cresol (p-cresol)	108.1	11.89	2.06	1	1	0.01752	-1.76	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol*.,29:677-683
21	4-n-butylaniline	149.24	9.51	3.1	1	1	0.411	-0.39	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
22	4-n-pentylaniline	163.3	9.79	3.59	1	1	0.226	-0.65	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
23	4-phenylbutanol	150	10.80	2.55	1	1	0.0862	-1.06	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
24	5-fluorouracil	130.01	13.46	-0.81	3	2	0.0000166	-4.78	0.002% aq. sodium azide solution	dermatomed 0.42 mm	abdomen	flow-through	0.002% aq. sodium azide solution	31	24	radiolabelled (3H)	*J.Investig.Pharmacol*., 94:235-240
25	adenosine	267.24	15.97	-1.05	9	4	0.000133	-3.88	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32(skin)	24	UV / VS	*Eur.J.Pharm.Sci*., 2006
26	aldosterone	360.45	12.31	1.63	4	2	5.80E-05	-4.24	not available	isol. epidermis	various	static	not available	26 (not available)	not available	radiolabelled	*J.Pharm.Sci*., 84:1144-1146
27	androstedione	288.42	10.03	2.75	2	0	0.00124	-2.91	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
28	aniline	93	10.83	1.08	1	1	6.10E-02	-1.21	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
29	atenolol	266.3	12.49	-0.03	4	3	0.00005	-4.30	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
30	benzene	78.12	9.19	1.99	0	0	0.111	-0.95	water	isol. epidermis	abdomen	static	0.1% NaCL solution	31 (skin)	4	HPLC	*J.Invest.Dermatol*.,85: 522-526
31	benzoic acid	122.1	11.94	1.87	1	1	0.00133	-2.88	deionised water	dermatomed 0.6 mm	not available	flow-through	PBS	37	48	radiolabelled (14C)	*J.Pharm.Sci*., 85:249-252
32	benzyl nicotinate	213.24	11.55	2.35	2	0	0.016	-1.80	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci*., 80:54-56
33	b-estradiol	272.4	11.90	3.94	2	2	0.01	-2.00	5% oleic acid, in 75% ethanol	dermatomed 0.5 mm	abdomen	static	5% oleic acid, in 75% ethanol	32	60	radiolabelled (3H)	*Pharm.Res.*, 10:1745-1750
34	betamethasone	392.45	12.37	2.02	6	3	0.000002	-5.70	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
35	bisoprolol	325.5	10.01	1.84	5	2	0.00027	-3.57	Sorensen's phosphate buffer (pH7.4)	dermatom. 1.2 mm	abdominal	flow-through	normal saline	32	72	HPLC	*Int.J.Pharm.*, 173:141-148
36	bisphenol A diglycidyl ether (BADGE)	340.8	10.38	3.84	4	0	4.80E-07	-6.32	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, BSA & gentamycin	32(skin)	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
37	boric acid	61.83	44.06	-0.22	3	3	0.0005	-3.30	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci*., 45: 42-51
38	butyl nicotinate	179.22	10.57	2.11	2	0	0.0166	-1.78	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37 (not available)	5	HPLC	*J.Pharm.Sci*., 80: 54-56
39	butyl paraben	194.23	11.45	3.47	2	1	0.056	-1.25	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci*., 96, No. 4, 2007
40	caffeine	194.2	32.83	0.16	4	0	0.00021	-3.68	ethylene glycol	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol*., 115:1-11
41	cannabidiol	314.46	11.11	8.01	2	2	0.00024	-3.62	propylene glycol : water (7:3) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol*., 56: 291-297
42	cannabinol	310.46	10.9	7.23	2	1	0.00015	-3.82	propylene glycol : water (7:3) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol*., 56: 291-297
43	celiprolol	379.5	11.51	1.93	5	3	0.00059	-3.23	Sorensen's phosphate buffer (pH7.4)	dermatom. 1.2 mm	abdominal	flow-through	normal saline	32	72	HPLC	*Int.J.Pharm.*, 173:141-148
44	chloroxylenol	156.6	11.20	3.25	1	1	0.05904	-1.23	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol*.,29:677-683
45	chlorpyrifos	350.59	10.10	4.66	1	0	0.00025	-3.60	commercial solution containing xylene & 111-TCE	full-thickness	breast	flow-through	50% aq. ethanol	32 (skin)	24	gas chromatography	*Hum.Exp.Toxicol*,19:104-107
46	cimetidine	252.34	12.86	0.4	6	3	0.000038	-4.42	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32 (skin)	24	radiolabelled	*Eur.J.Pharm.Sci*., 2006

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
47	clotrimazole	344.85	11.17	6.26	2	0	0.002	-2.70	propylene glycol	dermatom. 0.6 mm	abdomen	static	PBS ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*,215:51-56
48	codeine	299.4	12.09	1.28	4	1	0.000049	-4.31	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	24	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6:825-832
49	cortexolone	346.47	11.91	3.15	4	2	0.000075	-4.12	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52:63-70
50	corticosterone	346.5	11.91	1.99	4	2	0.00006	-4.22	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52:63-70
51	cortisone	360.5	12.1	1.81	5	2	0.00001	-5.00	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52:63-70
52	coumarin	146.15	11.91	1.51	1	0	0.0091	-2.04	phosphate buffer (pH 7.4)	full-thickness	abdomen	static	phosphate buffer (pH 7.4)	37	48	radiolabelled (14C)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
53	DDT	354.49	9.45	6.79	0	0	0.00594	-2.23	acetone	dermatomed 0.5 mm	abdomen	flow-through	Hanks HEPES buffered medium, 4% BSA & gentamycin	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 1225-1232
54	DEHP	390.57	9.39	8.39	2	0	0.0000057	-5.24	none	isol. epidermis	abdomen	static	50% aq. ethanol	30 (not available)	72	radiolabelled (14C)	*Environ.Health Perspect.*, 74:223-227
55	deoxyadenosine	251.24	15.49	-0.55	8	3	0.000129	-3.89	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32 (skin)	24	UV / VS	*Eur.J.Pharm.Sci.*, 2006
56	DEP	222.24	10.51	2.65	2	0	0.0000114	-4.94	none	isol. epidermis	abdomen	static	50% aq. ethanol	30 (not available)	30	radiolabelled (14C)	*Environ.Health Perspect.*, 74:223-227
57	diazinon	304.35	14.98	3.86	2	1	0.0095	-2.02	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, trizma, glucose	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8:1219-1224
58	dibutyl squarate	226.27	10.58	2.45	4	0	0.00002	-4.70	acetone	dermatomed skin	thigh	static	buffer	not given	48	UV spectroscopy	*Arch.Dermatol.Res.*, 280:57-60
59	dibutylphthalate	278.35	10.86	5.11	2	0	0.0000023	-5.64	none	isol. epidermis	abdomen	static	50% aq. ethanol	30 (not available)	30	radiolabelled (14C)	*Environ.Health Perspect.*, 74:223-227
60	dichlofenac	296.16	11.13	4.02	2	2	0.001	-3.00	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*, 170:129-133
61	diethyl squarate	170.16	11.50	4.07	4	0	0.00012	-3.92	acetone	dermatomed skin	thigh	static	buffer	not available	48	UV spectroscopy	*Arch.Dermatol.Res.*, 280:57-60
62	dimethylformamide	73.1	10.63	-0.93	1	0	0.0096	-2.02	none	full-thickness	abdomen	flow-through	physiological solution	37	4	gas chromatography	*Occup.Hyg.*, 1:191-198
63	dodecyl glycidyl ether (C12GE)	242.2	8.41	5.01	2	0	0.00000331	-5.48	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
64	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00000477	-5.32	ethanol	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm.*, 190: 155-164
65	estriol	288.4	12.95	2.81	3	3	0.00004	-4.40	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52: 63-70
66	estrone	270.4	11.55	3.43	2	1	0.0036	-2.44	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52: 63-70
67	ethanol	46.07	10.92	-0.14	1	1	0.000317	-3.50	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol.*, 96: 921-925
68	ethinyl estradiol	296.4	12.04	4	2	1	0.0000374	-4.43	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
69	ethyl nicotinate	151.17	11.06	1.13	2	2	0.00608	-2.22	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37(not available)	5	HPLC	*J.Pharm.Sci.*, 80:54-56
70	ethylaniline	121.2	9.73	2.11	1	1	0.288	-0.54	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
71	etodolac	287.26	10.86	3.93	3	2	0.00746	-2.13	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
72	etorphine	411.55	11.76	3.02	5	2	0.0036	-2.44	HCL & isotonic TRIS buffer	full-thickness	abdominal	static	isotonic TRIS buffer	37	24	radiolabelled (3H)	*Pharm.Res.*, 9: 963-965
73	fentanyl	336.5	10.30	3.89	2	0	0.0056	-2.25	physiological buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	9	GCL with Nitrogen selective detector	*Pharm.Res.*, 6: 825-832
74	flufenamic acid	281.2	10.96	4.88	5	2	0.0005499	-3.26	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
75	glyphosate	169.10	12.73	-4.47	3	4	0.000459	-3.34	water	dermatom. 1mm	not available	flow-through	PBS	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,34:731-735
76	griseofulvin	352.77	10.44	1.92	6	0	0.00194	-2.71	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
77	hydrocortisone	362.5	12.75	1.61	5	3	0.000158	-3.80	Britton-Robinson 0.2M buffers & ethanol, pH1	full-thickness	abdomen	flow-through	solution of NaCl & sodium azide	37	28	HPLC	*J.Contr.Release*, 76:327-335
78	hydromorphone	285.34	10.96	1.6	4	1	0.000015	-4.82	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	56	GLC with nitrogen selective detector	*Pharm.Res.*, 6: 825-832
79	hydroquinone	110.11	15.18	1.03	2	2	9.33E-06	-5.03	not available	isol. epidermis	abdomen	static	Dulbecco's PBS, antibiotics and fungicides	30	8	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016
80	ibuprofen	206.3	10.21	3.79	1	1	0.0363	-1.44	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
81	isosorbide dinitrate (ISDN)	236.14	10.36	0.76	4	0	0.00449	-2.35	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
82	ITF 296	238	12.91	1.61	3	0	0.00356	-2.45	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
83	ketoprofen	254.29	11.75	3.12	2	1	0.00062	-3.21	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
84	lidocaine	234.34	8.78	1.66	2	1	0.0106	-1.97	40% propylene glycol & HCL (pH10)	dermat. 0.15 mm	leg	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (14C)	*Int.J.Pharm.*, 71:167-173
85	lindane	290.83	8.54	4.26	0	0	0.0000059	-5.23	acetone	dermat. 0.23 mm	breast / abdomen	static	50% aq. ethanol	32 (skin)	24	gas chromatography	*Hum.Exp.Toxicol.*, 16: 652-657
86	linoleic acid	289.45	9.05	7.51	1	1	0.0000106	-4.97	ethanol	full-thickness	abdomen	static	phosphate buffer, pluronic F88 & BHT	37	95	radiolabelled (14C)	*J.Pharm.Pharmacol.*, 34:610-611
87	malathion	330.36	10.61	2.29	2	0	0.203	-0.69	aq. ethanol	dermat. 1mm	not available	flow-through	PBS	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,34:731-735
88	mannitol	182.17	18.63	-3.01	6	6	0.000025	-4.60	dist. water	isol. epidermis	abdomen	flow-through	0.9% physiological saline	32	48	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
89	meperidine	247.4	9.82	3.03	2	0	0.0037	-2.43	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	8	GLC with nitrogen selective detector	*Pharm.Res.* 6:825-832
90	methanol	32.04	11.68	-0.84	1	1	0.0016	-2.80	water	stratum corneum membrane	abdomen	static	WATER	22 (not available)	48	radiolabelled	*Int.J.Pharm.*, 18: 299-309
91	methiocarb	225.31	10.92	2.87	1	1	0.0011	-2.96	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*,48:697-701
92	methotrexate	454.45	15.05	-1.28	10	5	0.000113	-3.95	0.03M HCL % aq. propylene glycol (pH 1.98)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm.*, 25:65-75
93	methyl nicotinate	137.14	11.80	0.64	2	0	0.0034	-2.47	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*,80:54-56
94	methyl paraben	152.15	12.5	2	2	1	0.00000589	-5.23	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci.*, 96, No. 4, 2007
95	methyl parathion	263.21	10.45	2.75	1	0	0.000038	-4.42	20%MPA, 75% xylene, 5% dispersing agents	full-thickness	abdomen	static	saline, 4%BSA & gentamycin sulphate	32(skin)	48	gas chromatography	*Occup.Environ.Med.*,54:524-525
96	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00478	-2.32	water	dermatom. 0.32 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*,40:231-242
97	metoprolol	267.4	10.39	1.69	4	2	0.00083	-3.08	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
98	morphine	285.3	13.68	0.72	4	2	0.0000093	-5.03	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate phosphate buffer	37	52	GLC with nitrogen selective detector	*Pharmaceut.Res.*, 6: 825-832
99	naltrexone (NTX)	341	13.75	1.39	5	2	0.0095	-2.02	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
100	naproxene	230.3	11.42	3.1	2	1	0.00288	-2.54	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
101	n-hexyl nicotinate	207.27	10.49	3.1	2	0	0.0179	-1.75	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*,80:54-56
102	nicorandil	211.18	14.40	0.43	3	1	0.00005	-4.30	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci.*, 11:59-68

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
103	nicotine	162.3	11.25	1	2	0	0.0103	-1.99	0.05M phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	0.05M phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
104	nicotinic acid	123.11	13.23	0.69	2	1	0.000024	-4.62	water	isol. epidermis	abdomen / breast	static	isotonic PBS, NaCL	37	5	HPLC	*J.Pharm.Sci.*, 80:104-107
105	nikel	58.7	0	-0.57	0	0	0.00061	-3.21	synthetic sweat pH 6.5	full-thickness	abdomen	static	saline solution 0.9% NaCl	32(skin)	24	electrothermal spectrometry	*Toxicology Letters* 170 (2007), 49-56
106	nimesulide	308.31	15.25	2.22	3	2	0.00101	-3.00	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
107	nizatidine	331.45	12.36	-0.43	5	2	0.000038	-4.43	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
108	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00224	-2.65	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 7:141-148
109	n-nitrosodiethanolamine	134.13	15.67	-1.28	4	2	0.0041	-2.39	isoprpyl myristate + sucrose (3H)	isol. epidermis	abdomen	static	PBS	32 (skin)	48	radiolabelled (14C)	*Food Chem.Toxicol.*,33:315-322
110	n-octanol	130.23	9.45	2.81	1	1	0.061	-1.21	water	strarum corneum	abdomen	static	water	22 (not available)	48	radiolabelled (14C)	*Int.J.Pharm.*, 18:299-309
111	nonane	128.3	7.51	4.76	0	0	0.000042	-4.38	JP-8	dermatom.0.56 mm	back	static	6% Volpo20 in PBS	32 (skin)	4	GC	*Toxicol.Sci.*, 55:247-255
112	NTX-3 heptanoate (HEP-NTX)	453	11.44	3.92	5	1	0.0009	-3.05	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
113	NTX-3-acetate (ACE-NTX)	383	12.96	1.47	5	1	0.0077	-2.11	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
114	NTX-3-butyrate (BUT-NTX)	411	11.88	2.45	5	1	0.0013	-2.89	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
115	NTX-3-hexanoate (HEX-NTX)	439	11.57	2.94	5	1	0.0012	-2.92	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
116	NTX-3-propionate (PROP-NTX)	397	12.06	1.96	5	1	0.0025	-2.60	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
117	NTX-3-valerate (VAL-NTX)	425	11.72	2.45	5	1	0.0007	-3.15	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci.*,91: 2571-2578
118	o-cresyl glycidyl ether (oCGE)	164.2	10.38	2.16	2	0	9.30E-05	-4.03	acetone	dermatommed	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*,30:469-483
119	oxprenolol	265.4	10.52	1.83	4	2	0.00154	-2.81	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
120	paraquat	257.16	10.45	-2.71	0	0	0.0000087	-5.06	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol.*, 96:921-925
121	parathion	291.26	10.76	3.73	1	0	0.000189	-3.72	none	dermatom. 0.5 mm	back	flow-through	Eagles-MEM-BSS & gentamycin	37	96	radiolabelled	*Toxicol.Appl.Pharmacol.*, 168:149-152
122	phenol	94.11	12.33	1.51	1	1	0.00822	-2.09	dist. water	isol. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
123	pirimicarb	238.29	11.05	1.4	4	0	0.0027	-2.57	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*,48:697-701
124	prednisolone	360.44	12.96	1.49	5	3	0.0000235	-4.63	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
125	prednisone	358.44	12.71	1.46	5	2	0.0000246	-4.61	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
126	pregnenolone	316.5	10.36	3.89	2	1	0.0015	-2.82	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52:63-70
127	prochloraz	376.7	10.69	4.13	3	0	0.0007	-3.15	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*,48:697-701
128	progesterone	314.5	10.05	3.67	2	0	0.03	-1.52	not available	isol. epidermis	various	static	not available	37 (not available)	not available	radiolabelled (14C)	J.Pharm. Sci., 84:1144-1146
129	propoxur	209.25	10.31	1.9	2	1	0.000885	-3.05	60% aq. ethanol	full-thickness	abdomen	static	culture medium & 10% fetal bovine serum	32	24	radiolabelled (14C)	*Toxicol.Sci.*, 58:15-22
130	propranolol	295.3	11.13	2.6	3	2	0.00178	-2.75	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
131	ranitidine	314.1	11.41	0.29	5	2	0.0000887	-4.05	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
132	resorcinol	110.11	15.18	1.03	2	2	0.00024	-3.62	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
133	salicylic acid	138.1	14.39	2.24	2	2	0.0131	-1.89	phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
134	squaric acid	114.06	20.47	-0.44	4	2	0.0000075	-5.12	acetone	dermatom.	thigh	static	buffer	not available	48	UV spectroscopy	*Arch.Dermatol.Res.*,280:57-60
135	sufentanil	386.6	10.47	3.62	3	0	0.012	-1.92	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate phosphate buffer	37	8.5	GLC with nitrogen selective detector	*Pharm.Res,*6:825-832
136	terbinafine	291.4	9.33	5.81	1	0	0.001	-3.00	propylene glycol	dermatomed 0.6 mm	abdomen	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*,215:51-56
137	testosterone	288.4	10.66	3.27	2	1	0.00671	-2.17	water gel	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115:1-11
138	theophylline	180.17	14.05	-0.39	4	1	0.000432	-3.36	water	dermatomed 0.2 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*, 40:231-242
139	thymol	150.2	10.81	3.52	1	1	0.0528	-1.28	dist. water	isol. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
140	triclosan	289.55	10.02	2.47	2	1	0.000034	-4.47	methanol and adhesive Durotak 387-2051	isol. epidermis	breast and abdomen	static	ethanol & PBS	37	12	HPLC	*Int.J.Pharm.*,235:229-236
141	water	18.02	26.68	-1.38	1	1	0.000707	-3.15	saline	dermatomed 0.13 mm	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro,* 8:827-830
142	Δ-tetrahydrocannabinol (THC)	314.46	9.75	7.6	2	1	0.000028	-4.55	propylene glycol : water : ethanol (9:1:1) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol.*, 56: 291-297
143	borax	201.22	not calc.	not calc.	0	0	0.00017	-3.77	water	dermatom.0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*,45:42-51
144	epikote YX4000	354.4	11.00	5.19	4	0	0.000000047	-7.33	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica,* 30:469-483
145	erioglaucine	793.86	not calc.	-1.5	not calc.	not calc.	0.00000136	-5.87	40% propylene glycol	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*,42: 468-472

Group A18

Type of skin: human Site: all types All temperatures Time Any analytical tool Vehicle: any Receptor fluid any

No duplicates

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	1,6-hexanediol diglycidyl ether (HDDGE)	230.2	9.36	0.84	4	0	0.000136	-3.87	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32(skin)	24	radiolabelled (14C)	*Xenobiotica,* 30:469-483
2	1-methoxylpropan-2-ol	90.12	10.16	-0.49	2	1	0.00065	-3.19	none	dermatom. 0.5 mm	breast	flow-through	Eagles MEM & sodium carbonate & gentamycin	32	24	radiolabelled (14C)	*Int.Arch.Occup.Environ.Health,* 75:519-527
3	2-(2-butoxyethoxy) ethanol	162.23	9.74	0.29	3	1	0.0000357	-4.45	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
4	2-(2-ethoxyethoxy) ethanol	134.18	10.04	-0.69	3	1	0.000132	-3.88	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
5	2-(2-methoxyethoxy) ethanol	120.15	10.25	-1.18	3	1	0.000206	-3.69	none	isol. epidermis	abdomen	static	dist. water	30(not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
6	2,4 dimethylamine	266.13	9.52	0.84	3	2	0.000945	-3.02	commercial formulation clean crop	dermatom.0.3 mm	abdomen	flow-through	HBSS, HEPES, buffer BSA & gentamycin sulphate	37	48	radiolabelled (14C)	*Toxicol.Vitro,*11:251-262
7	2-butoxyethanol	118.18	9.88	0.57	2	1	0.000214	-3.67	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
8	2-cresol (o-cresol)	108.1	11.89	2.06	1	1	0.01572	-1.80	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
9	2-ethoxyethanol	90.12	10.33	-0.42	2	1	0.000842	-3.07	none	full-thickness	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
10	2-ethoxyethyl acetate	132.16	9.22	0.59	2	0	0.000807	-3.09	none	isol. epidermis	abdomen	static	dist. water	30 (not available)	8	GC with flame ionisation	*Environ.Health Perspect.*, 57:193-197
11	2-methoxyethanol	76.01	10.67	-0.91	2	1	0.00289	-2.54	none	isol. epidermis	abdomen	static	dist. water	30(not available)	8	GC with flame ionisation	*Environ.Health Perspect*,57:193-197
12	2-naphthol	144.16	12.69	2.69	1	1	0.0279	-1.55	dist. water	isol. epidermis	abdomen	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
13	2-phenoxyethanol	138.17	11.49	1.1	2	1	0.001337	-2.87	methanol	dermat.0.33	breast / abdomen / leg	flow-through	MEM & penicillin / streptomycin +CO2	37	6	HPLC	*Food Chem.Toxicol.*,35:1009-1016
14	2-phenylethanol	122.2	11.38	1.57	1	1	0.031	-1.51	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
15	2-phenylphenol	170.21	12.24	3.28	1	1	0.0183	-1.74	60% aq. ethanol	isol. epidermis	abdomen	static	saline (0.9% NaCL), 0.01% sodium azide & 3% BSA	32	8	radiolabelled (14C)	*Regul.Toxicol.Pharmacol.*, 35:198-208
16	3,4 xylenol	202.55	11.54	2.61	1	1	0.036	-1.44	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
17	3-cresol (m-cresol)	108.14	11.89	2.06	1	1	0.01524	-1.82	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
18	3-nitrophenol	139.1	13.02	1.91	2	1	0.00564	-2.25	dist. water	isol. epidermis	abdomen	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
19	4-bromophenol	173.01	11.48	2.4	1	1	0.03612	-1.44	dist. water	isol. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
20	4-cresol (p-cresol)	108.1	11.89	2.06	1	1	0.01752	-1.76	dist. water	isolated epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
21	4-n-butylaniline	149.24	9.51	3.1	1	1	0.411	-0.39	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
22	4-n-pentylaniline	163.3	9.79	3.59	1	1	0.226	-0.65	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
23	4-phenylbutanol	150	10.80	2.55	1	1	0.0862	-1.06	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
24	5-fluorouracil	130.01	13.46	-0.81	3	2	0.0000166	-4.78	0.002% aq. sodium azide solution	dermatomed 0.42 mm	abdomen	flow-through	0.002% aq. sodium azide solution	31	24	radiolabelled (3H)	*J.Investig.Pharmacol.*, 94:235-240
25	adenosine	267.24	15.97	-1.05	9	4	0.000133	-3.88	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32(skin)	24	UV / VS	*Eur.J.Pharm.Sci.*, 2006
26	aldosterone	360.45	12.31	1.63	4	2	5.80E-05	-4.24	not available	isol. epidermis	various	static	not available	26 (not available)	not available	radiolabelled	*J.Pharm.Sci.*, 84:1144-1146
27	androstedione	288.42	10.03	2.75	2	0	0.00124	-2.91	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
28	aniline	93	10.83	1.08	1	1	6.10E-02	-1.21	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
29	atenolol	266.3	12.49	-0.03	4	3	0.00005	-4.30	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
30	benzene	78.12	9.19	1.99	0	0	0.111	-0.95	water	isol. epidermis	abdomen	static	0.1% NaCL solution	31 (skin)	4	HPLC	*J.Invest.Dermatol.*,85: 522-526
31	benzoic acid	122.1	11.94	1.87	1	1	0.00133	-2.88	deionised water	dermatomed 0.6 mm	not available	flow-through	PBS	37	48	radiolabelled (14C)	*J.Pharm.Sci.*, 85:249-252
32	benzyl nicotinate	213.24	11.55	2.35	2	0	0.016	-1.80	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci.*, 80:54-56
33	b-estradiol	272.4	11.90	3.94	2	2	0.01	-2.00	5% oleic acid, in 75% ethanol	dermatomed 0.5 mm	abdomen	static	5% oleic acid, in 75% ethanol	32	60	radiolabelled (3H)	*Pharm.Res.*, 10:1745-1750
34	betamethasone	392.45	12.37	2.02	6	3	0.000002	-5.70	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
35	bisoprolol	325.5	10.01	1.84	5	2	0.00027	-3.57	Sorensen's phosphate buffer (pH7.4)	dermatom. 1.2 mm	abdominal	flow-through	normal saline	32	72	HPLC	*Int.J.Pharm.*, 173:141-148
36	bisphenol A diglycidyl ether (BADGE)	340.8	10.38	3.84	4	0	4.80E-07	-6.32	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, BSA & gentamycin	32(skin)	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
37	boric acid	61.83	44.06	-0.22	3	3	0.0005	-3.30	water	dermatomed 0.5 mm	thigh	flow-through	PBS	32(skin)	24	radiolabelled (10B) & CPMS	*Toxicol.Sci.*, 45: 42-51

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
38	butyl nicotinate	179.22	10.57	2.11	2	0	0.0166	-1.78	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37 (not available)	5	HPLC	*J.Pharm.Sci*., 80: 54-56
39	butyl paraben	194.23	11.45	3.47	2	1	0.056	-1.25	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci*., 96, No. 4, 2007
40	caffeine	194.2	32.83	0.16	4	0	0.00021	-3.68	ethylene glycol	dermatomed 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (14C)	*J.Dermatol*., 115:1-11
41	cannabidiol	314.46	11.11	8.01	2	2	0.00024	-3.62	propylene glycol : water (7:3) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol*., 56: 291-297
42	cannabinol	310.46	10.9	7.23	2	1	0.00015	-3.82	propylene glycol : water (7:3) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol*., 56: 291-297
43	celiprolol	379.5	11.51	1.93	5	3	0.00059	-3.23	Sorensen's phosphate buffer (pH7.4)	dermatom. 1.2 mm	abdominal	flow-through	normal saline	32	72	HPLC	*Int.J.Pharm*., 173:141-148
44	chloroxylenol	156.6	11.20	3.25	1	1	0.05904	-1.23	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol*.,29:677-683
45	chlorpyrifos	350.59	10.10	4.66	1	0	0.00025	-3.60	commercial solution containing xylene & 111-TCE	full-thickness	breast	flow-through	50% aq. ethanol	32 (skin)	24	gas chromatography	*Hum.Exp.Toxicol*,19:104-107
46	cimetidine	252.34	12.86	0.4	6	3	0.000038	-4.42	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32 (skin)	24	radiolabelled	*Eur.J.Pharm.Sci*., 2006
47	clotrimazole	344.85	11.17	6.26	2	0	0.002	-2.70	propylene glycol	dermatom. 0.6 mm	abdomen	static	PBS ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm*.,215:51-56
48	codeine	299.4	12.09	1.28	4	1	0.000049	-4.31	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	24	GLC with nitrogen selective detector	*Pharmaceut.Res*., 6:825-832
49	cortexolone	346.47	11.91	3.15	4	2	0.000075	-4.12	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol*., 52:63-70
50	corticosterone	346.5	11.91	1.99	4	2	0.00006	-4.22	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol*., 52:63-70
51	cortisone	360.5	12.1	1.81	5	2	0.00001	-5.00	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol*., 52:63-70
52	coumarin	146.15	11.91	1.51	1	0	0.0091	-2.04	phosphate buffer (pH 7.4)	full-thickness	abdomen	static	phosphate buffer (pH 7.4)	37	48	radiolabelled (14C)	*Meth. and Find Exp.Clin.Pharmacol*., 11:643-646
53	DDT	354.49	9.45	6.79	0	0	0.00594	-2.23	acetone	dermatomed 0.5 mm	abdomen	flow-through	Hanks HEPES buffered medium, 4% BSA & gentamycin	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8: 1225-1232
54	DEHP	390.57	9.39	8.39	2	0	0.0000057	-5.24	none	isol. epidermis	abdomen	static	50% aq. ethanol	30 (not available)	72	radiolabelled (14C)	*Environ.Health Perspect*., 74:223-227
55	deoxyadenosine	251.24	15.49	-0.55	8	3	0.000129	-3.89	PBS	full-thickness	abdomen	static	aq. solution, 0.002% sodium azide	32 (skin)	24	UV / VS	*Eur.J.Pharm.Sci*., 2006
56	DEP	222.24	10.51	2.65	2	0	0.0000114	-4.94	none	isol. epidermis	abdomen	static	50% aq. ethanol	30 (not available)	30	radiolabelled (14C)	*Environ.Health Perspect*., 74:223-227
57	diazinon	304.35	14.98	3.86	2	1	0.0095	-2.02	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, trizma, glucose	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8:1219-1224
58	dibutyl squarate	226.27	10.58	2.45	4	0	0.00002	-4.70	acetone	dermatomed skin	thigh	static	buffer	not given	48	UV spectroscopy	*Arch.Dermatol.Res*., 280:57-60
59	dibutylphthalate	278.35	10.86	5.11	2	0	0.0000023	-5.64	none	isol. epidermis	abdomen	static	50% aq. ethanol	30 (not available)	30	radiolabelled (14C)	*Environ.Health Perspect*., 74:223-227
60	dichlofenac	296.16	11.13	4.02	2	2	0.001	-3.00	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm*., 170:129-133
61	diethyl squarate	170.16	11.50	4.07	4	0	0.00012	-3.92	acetone	dermatomed skin	thigh	static	buffer	not available	48	UV spectroscopy	*Arch.Dermatol.Res*., 280:57-60
62	dimethylformamide	73.1	10.63	-0.93	1	0	0.0096	-2.02	none	full-thickness	abdomen	flow-through	physiological solution	37	4	gas chromatography	*Occup.Hyg*., 1:191-198
63	dodecyl glycidyl ether (C12GE)	242.2	8.41	5.01	2	0	0.00000331	-5.48	acetone	dermatomed skin	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
64	doxycycline HCL	444.44	16.55	-1.36	9	6	0.00000477	-5.32	ethanol	full-thickness	not available	static	PBS pH 7.4	37	48	HPLC	*Int.Journal of Pharm*., 190: 155-164
65	estriol	288.4	12.95	2.81	3	3	0.00004	-4.40	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol*., 52: 63-70

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
66	estrone	270.4	11.55	3.43	2	1	0.0036	-2.44	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol*., 52: 63-70
67	ethanol	46.07	10.92	-0.14	1	1	0.000317	-3.50	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol*., 96: 921-925
68	ethinyl estradiol	296.4	12.04	4	2	1	0.0000374	-4.43	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
69	ethyl nicotinate	151.17	11.06	1.13	2	2	0.00608	-2.22	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37(not available)	5	HPLC	*J.Pharm.Sci*., 80:54-56
70	ethylaniline	121.2	9.73	2.11	1	1	0.288	-0.54	buffered solution pH 6.2	epidermis	abdomen	static	saline solution buffer (pH 7.4) + polysorbate 80	37	36	not available	*I.J.Pharmac.* 129: 33-40
71	etodolac	287.26	10.86	3.93	3	2	0.00746	-2.13	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
72	etorphine	411.55	11.76	3.02	5	2	0.0036	-2.44	HCL & isotonic TRIS buffer	full-thickness	abdominal	static	isotonic TRIS buffer	37	24	radiolabelled (3H)	*Pharm.Res*., 9: 963-965
73	fentanyl	336.5	10.30	3.89	2	0	0.0056	-2.25	physiological buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	9	GCL with Nitrogen selective detector	*Pharm.Res*., 6: 825-832
74	flufenamic acid	281.2	10.96	4.88	5	2	0.0005499	-3.26	wool alcohols ointment	dermatom. 0.075 mm	abdomen	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	*J.Contr.Rel.*, 75:283-295
75	glyphosate	169.10	12.73	-4.47	3	4	0.000459	-3.34	water	dermatom. 1mm	not available	flow-through	PBS	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,34:731-735
76	griseofulvin	352.77	10.44	1.92	6	0	0.00194	-2.71	phosphate buffer	full-thickness	abdomen	static	phosphate buffer	37	48	radiolabelled (3H)	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
77	hydrocortisone	362.5	12.75	1.61	5	3	0.000158	-3.80	Britton-Robinson 0.2M buffers & ethanol, pH1	full-thickness	abdomen	flow-through	solution of NaCl & sodium azide	37	28	HPLC	*J.Contr.Release*, 76:327-335
78	hydromorphone	285.34	10.96	1.6	4	1	0.000015	-4.82	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	56	GLC with nitrogen selective detector	*Pharm.Res*., 6: 825-832
79	hydroquinone	110.11	15.18	1.03	2	2	9.33E-06	-5.03	not available	isol. epidermis	abdomen	static	Dulbecco's PBS, antibiotics and fungicides	30	8	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016
80	ibuprofen	206.3	10.21	3.79	1	1	0.0363	-1.44	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm.*,170:129-133
81	isosorbide dinitrate (ISDN)	236.14	10.36	0.76	4	0	0.00449	-2.35	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci*., 11:59-68
82	ITF 296	238	12.91	1.61	3	0	0.00356	-2.45	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci*., 11:59-68
83	ketoprofen	254.29	11.75	3.12	2	1	0.00062	-3.21	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
84	lidocaine	234.34	8.78	1.66	2	1	0.0106	-1.97	40% propylene glycol & HCL (pH10)	dermat. 0.15 mm	leg	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (14C)	*Int.J.Pharm*., 71:167-173
85	lindane	290.83	8.54	4.26	0	0	0.0000059	-5.23	acetone	dermat. 0.23 mm	breast / abdomen	static	50% aq. ethanol	32 (skin)	24	gas chromatography	*Hum.Exp.Toxicol*., 16: 652-657
86	linoleic acid	289.45	9.05	7.51	1	1	0.0000106	-4.97	ethanol	full-thickness	abdomen	static	phosphate buffer, pluronic F88 & BHT	37	95	radiolabelled (14C)	*J.Pharm.Pharmacol*., 34:610-611
87	malathion	330.36	10.61	2.29	2	0	0.203	-0.69	aq. ethanol	dermat. 1mm	not available	flow-through	PBS	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,34:731-735
88	mannitol	182.17	18.63	-3.01	6	6	0.000025	-4.60	dist. water	isol. epidermis	abdomen	flow-through	0.9% physiological saline	32	48	radiolabelled (14C)	*Toxicol.Vitro*, 8:827-830
89	meperidine	247.4	9.82	3.03	2	0	0.0037	-2.43	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate-phosphate buffer	37	8	GLC with nitrogen selective detector	*Pharm.Res.* 6:825-832
90	methanol	32.04	11.68	-0.84	1	1	0.0016	-2.80	water	stratum corneum membrane	abdomen	static	WATER	22 (not available)	48	radiolabelled	*Int.J.Pharm*., 18: 299-309
91	methiocarb	225.31	10.92	2.87	1	1	0.0011	-2.96	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*,48:697-701
92	methotrexate	454.45	15.05	-1.28	10	5	0.000113	-3.95	0.03M HCL % aq. propylene glycol (pH 1.98)	full-thickness	abdomen	static	saline	37	not available	HPLC	*Int.J.Pharm*., 25:65-75
93	methyl nicotinate	137.14	11.80	0.64	2	0	0.0034	-2.47	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci*.,80:54-56

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
94	methyl paraben	152.15	12.5	2	2	1	0.00000589	-5.23	PBS	epidermis	abdomen	static	PBS pH 7.4	37	10	HPLC	*J.Pharm.Sci*., 96, No. 4, 2007
95	methyl parathion	263.21	10.45	2.75	1	0	0.000038	-4.42	20%MPA, 75% xylene, 5% dispersing agents	full-thickness	abdomen	static	saline, 4%BSA & gentamycin sulphate	32(skin)	48	gas chromatography	*Occup.Environ.Med*.,54:524-525
96	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	0.00478	-2.32	water	dermatom. 0.32 mm	dorsal	flow-through	normal saline & 0.25% w/v chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem*.,40:231-242
97	metoprolol	267.4	10.39	1.69	4	2	0.00083	-3.08	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm*., 194: 249-259
98	morphine	285.3	13.68	0.72	4	2	0.0000093	-5.03	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate phosphate buffer	37	52	GLC with nitrogen selective detector	*Pharmaceut.Res*., 6: 825-832
99	naltrexone (NTX)	341	13.75	1.39	5	2	0.0095	-2.02	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci*.,91: 2571-2578
100	naproxene	230.3	11.42	3.1	2	1	0.00288	-2.54	water	full-thickness	abdomen	static	PBS	37	72	HPLC	*Int.J.Pharm*.,170:129-133
101	n-hexyl nicotinate	207.27	10.49	3.1	2	0	0.0179	-1.75	water	isol. epidermis	abdomen / breast	static	isotonic PBS and NaCL	37	5	HPLC	*J.Pharm.Sci*.,80:54-56
102	nicorandil	211.18	14.40	0.43	3	1	0.00005	-4.30	water : propylene glycol (80:20 v/v) solution	SCE	abdomen	flow-through	PBS : propylene glycol (80:20 v/v) solution	37	24	RP HPLC	*Eur.J.Pharm.Sci*., 11:59-68
103	nicotine	162.3	11.25	1	2	0	0.0103	-1.99	0.05M phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	0.05M phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm.Sci*., 11:59-68
104	nicotinic acid	123.11	13.23	0.69	2	1	0.000024	-4.62	water	isol. epidermis	abdomen / breast	static	isotonic PBS, NaCL	37	5	HPLC	*J.Pharm.Sci*., 80:104-107
105	nikel	58.7	0	-0.57	0	0	0.00061	-3.21	synthetic sweat pH 6.5	full-thickness	abdomen	static	saline solution 0.9% NaCl	32(skin)	24	electrothermal spectrometry	*Toxicology Letters* 170 (2007), 49-56
106	nimesulide	308.31	15.25	2.22	3	2	0.00101	-3.00	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
107	nizatidine	331.45	12.36	-0.43	5	2	0.000038	-4.43	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
108	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.00224	-2.65	acetone	dermatomed 0.5 mm	abdomen	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 7:141-148
109	n-nitrosodiethanolamine	134.13	15.67	-1.28	4	2	0.0041	-2.39	isoprpyl myristate + sucrose (3H)	isol. epidermis	abdomen	static	PBS	32 (skin)	48	radiolabelled (14C)	*Food Chem.Toxicol*.,33:315-322
110	n-octanol	130.23	9.45	2.81	1	1	0.061	-1.21	water	strarum corneum	abdomen	static	water	22 (not available)	48	radiolabelled (14C)	*Int.J.Pharm.*, 18:299-309
111	nonane	128.3	7.51	4.76	0	0	0.000042	-4.38	JP-8	dermatom.0.56 mm	back	static	6% Volpo20 in PBS	32 (skin)	4	GC	*Toxicol.Sci*., 55:247-255
112	NTX-3 heptanoate (HEP-NTX)	453	11.44	3.92	5	1	0.0009	-3.05	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci*.,91: 2571-2578
113	NTX-3-acetate (ACE-NTX)	383	12.96	1.47	5	1	0.0077	-2.11	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci*.,91: 2571-2578
114	NTX-3-butyrate (BUT-NTX)	411	11.88	2.45	5	1	0.0013	-2.89	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci*.,91: 2571-2578
115	NTX-3-hexanoate (HEX-NTX)	439	11.57	2.94	5	1	0.0012	-2.92	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci*.,91: 2571-2578
116	NTX-3-propionate (PROP-NTX)	397	12.06	1.96	5	1	0.0025	-2.60	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci*.,91: 2571-2578
117	NTX-3-valerate (VAL-NTX)	425	11.72	2.45	5	1	0.0007	-3.15	light mineral oil	dermatomed 0.2 mm	abdominal	flow-through	isotonic phosphate buffer pH 7.4	32	24	HPLC	*J.Pharm.Sci*.,91: 2571-2578
118	o-cresyl glycidyl ether (oCGE)	164.2	10.38	2.16	2	0	9.30E-05	-4.03	acetone	dermatommed	breast	flow-through	HBSS, HEPES, buffer BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*,30:469-483
119	oxprenolol	265.4	10.52	1.83	4	2	0.00154	-2.81	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm*., 194: 249-259
120	paraquat	257.16	10.45	-2.71	0	0	0.0000087	-5.06	water	full-thickness	abdomen	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol*., 96:921-925
121	parathion	291.26	10.76	3.73	1	0	0.000189	-3.72	none	dermatom. 0.5 mm	back	flow-through	Eagles-MEM-BSS & gentamycin	37	96	radiolabelled	*Toxicol.Appl.Pharmacol*., 168:149-152

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
122	phenol	94.11	12.33	1.51	1	1	0.00822	-2.09	dist. water	isol. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
123	pirimicarb	238.29	11.05	1.4	4	0	0.0027	-2.57	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*,48:697-701
124	prednisolone	360.44	12.96	1.49	5	3	0.0000235	-4.63	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
125	prednisone	358.44	12.71	1.46	5	2	0.0000246	-4.61	40% PEG sol.	full-thickness	not available	static	40% PEG sol.	37	not available	HPLC	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
126	pregnenolone	316.5	10.36	3.89	2	1	0.0015	-2.82	water	isol. epidermis	not available	static	aq. penicillin / streptomycin	26 (not available)	not available	radiolabelled (14C)	*J.Investig.Dermatol.*, 52:63-70
127	prochloraz	376.7	10.69	4.13	3	0	0.0007	-3.15	aq. solutions 0.9% NaCL, 2% ethanol	dermatom. 0.6-0.9 mm	breast	flow-through	aq. solution, 0.9% NaCL, 5% BSA	32 (skin)	48	HPLC	*Ann.Occup.Hyg.*,48:697-701
128	progesterone	314.5	10.05	3.67	2	0	0.03	-1.52	not available	isol. epidermis	various	static	not available	37 (not available)	not available	radiolabelled (14C)	J.Pharm. Sci., 84:1144-1146
129	propoxur	209.25	10.31	1.9	2	1	0.000885	-3.05	60% aq. ethanol	full-thickness	abdomen	static	culture medium & 10% fetal bovine serum	32	24	radiolabelled (14C)	*Toxicol.Sci.*, 58:15-22
130	propranolol	295.3	11.13	2.6	3	2	0.00178	-2.75	Sorensen's phosphate buffer (pH7.4)	dermatomed 1.2 mm	abdominal	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	72	HPLC	*Int.J.Pharm.*, 194: 249-259
131	ranitidine	314.1	11.41	0.29	5	2	0.0000887	-4.05	not available	full-thickness	abdomen	static	isotonic saline phosphate buffer solution	37	not available	HPLC	*J.Pharm.Sci*ence, 92:3:656-664
132	resorcinol	110.11	15.18	1.03	2	2	0.00024	-3.62	dist. water	isol. epidermis	abdominal	static	dist. water	25	8	spectrophotometry	*J.Pharm.Pharmacol.*,29:677-683
133	salicylic acid	138.1	14.39	2.24	2	2	0.0131	-1.89	phosphate buffer	dermatom. 0.41 mm	abdomen / breast	static	phosphate buffer	32 (skin)	28	HPLC	*Eur.J.Pharm.Sci.*, 11:59-68
134	squaric acid	114.06	20.47	-0.44	4	2	0.0000075	-5.12	acetone	dermatom.	thigh	static	buffer	not available	48	UV spectroscopy	*Arch.Dermatol.Res.*,280:57-60
135	sufentanil	386.6	10.47	3.62	3	0	0.012	-1.92	physiological phosphate buffer	isol. epidermis	abdomen	static	citrate phosphate buffer	37	8.5	GLC with nitrogen selective detector	*Pharm.Res,*6:825-832
136	terbinafine	291.4	9.33	5.81	1	0	0.001	-3.00	propylene glycol	dermatomed 0.6 mm	abdomen	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*,215:51-56
137	testosterone	288.4	10.66	3.27	2	1	0.00671	-2.17	water gel	dermatom. 0.35 mm	abdomen	flow-through	saline	32 (skin)	36	radiolabelled (3H)	*J.Dermatol.*,115:1-11
138	theophylline	180.17	14.05	-0.39	4	1	0.000432	-3.36	water	dermatomed 0.2 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC	*J.Soc.Cosmet.Chem.*, 40:231-242
139	thymol	150.2	10.81	3.52	1	1	0.0528	-1.28	dist. water	isol. epidermis	abdominal	static	dist. water	25 (not available)	8	spectrophotometry	*J.Pharm.Pharmacol.*, 29:677-683
140	triclosan	289.55	10.02	2.47	2	1	0.000034	-4.47	methanol and adhesive Durotak 387-2051	isol. epidermis	breast and abdomen	static	ethanol & PBS	37	12	HPLC	*Int.J.Pharm.*,235:229-236
141	water	18.02	26.68	-1.38	1	1	0.000707	-3.15	saline	dermatomed 0.13 mm	abdomen	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8:827-830
142	Δ-tetrahydrocannabinol (THC)	314.46	9.75	7.6	2	1	0.000028	-4.55	propylene glycol : water : ethanol (9:1:1) & 4% BSA	dermatom. 0.2 mm	abdomen	flow-through	HHBSS, BSA, HEPES buffered-Hank's balanced salt solution & gentamycin	32 (skin)	48	RP HPLC	*Pharm.Pharmacol.*, 56: 291-297

Group A19

Type of skin: human Site: all types All temperatures Time Any analytical tool Vehicle: any Receptor fluid any

No duplicates

No	Name	MW	SP ($(cal/cm^3)^{1/2}$)	Log P KOWWIN	Ha	Hd	Log K_p (cmh^{-1})	Journal
1	1,6-hexanediol diglycidyl ether (HDDGE)	230.2	9.36	0.84	4	0	-3.87	*Xenobiotica*, 30:469-483
2	1-methoxylpropan-2-ol	90.12	10.16	-0.49	2	1	-3.19	*Int.Arch.Occup.Environ.Health*, 75:519-527
3	2-(2-butoxyethoxy) ethanol	162.23	9.74	0.29	3	1	-4.45	*Environ.Health Perspect.*, 57:193-197

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	Log K_p (cmh^{-1})	Journal
4	2-(2-ethoxyethoxy) ethanol	134.18	10.04	-0.69	3	1	-3.88	*Environ.Health Perspect.*, 57:193-197
5	2-(2-methoxyethoxy) ethanol	120.15	10.25	-1.18	3	1	-3.69	*Environ.Health Perspect.*, 57:193-197
6	2,4 dimethylamine	266.13	9.52	0.84	3	2	-3.02	*Toxicol.Vitro*,11:251-262
7	2-butoxyethanol	118.18	9.88	0.57	2	1	-3.67	*Environ.Health Perspect.*, 57:193-197
8	2-cresol (o-cresol)	108.1	11.89	2.06	1	1	-1.80	*J.Pharm.Pharmacol.*,29:677-683
9	2-ethoxyethanol	90.12	10.33	-0.42	2	1	-3.07	*Environ.Health Perspect.*, 57:193-197
10	2-ethoxyethyl acetate	132.16	9.22	0.59	2	0	-3.09	*Environ.Health Perspect.*, 57:193-197
11	2-methoxyethanol	76.01	10.67	-0.91	2	1	-2.54	*Environ.Health Perspect*,57:193-197
12	2-naphthol	144.16	12.69	2.69	1	1	-1.55	*J.Pharm.Pharmacol.*, 29:677-683
13	2-phenoxyethanol	138.17	11.49	1.1	2	1	-2.87	*Food Chem.Toxicol.*,35:1009-1016
14	2-phenylethanol	122.2	11.38	1.57	1	1	-1.51	*I.J.Pharmac.* 129: 33-40
15	2-phenylphenol	170.21	12.24	3.28	1	1	-1.74	*Regul.Toxicol.Pharmacol.*, 35:198-208
16	3,4 xylenol	202.55	11.54	2.61	1	1	-1.44	*J.Pharm.Pharmacol.*,29:677-683
17	3-cresol (m-cresol)	108.14	11.89	2.06	1	1	-1.82	*J.Pharm.Pharmacol.*,29:677-683
18	3-nitrophenol	139.1	13.02	1.91	2	1	-2.25	*J.Pharm.Pharmacol.*,29:677-683
19	4-bromophenol	173.01	11.48	2.4	1	1	-1.44	*J.Pharm.Pharmacol.*, 29:677-683
20	4-cresol (p-cresol)	108.1	11.89	2.06	1	1	-1.76	*J.Pharm.Pharmacol.*,29:677-683
21	4-n-butylaniline	149.24	9.51	3.1	1	1	-0.39	*I.J.Pharmac.* 129: 33-40
22	4-n-pentylaniline	163.3	9.79	3.59	1	1	-0.65	*I.J.Pharmac.* 129: 33-40
23	4-phenylbutanol	150	10.80	2.55	1	1	-1.06	*I.J.Pharmac.* 129: 33-40
24	5-fluorouracil	130.01	13.46	-0.81	3	2	-4.78	*J.Investig.Pharmacol.*, 94:235-240
25	adenosine	267.24	15.97	-1.05	9	4	-3.88	*Eur.J.Pharm.Sci.*, 2006
26	aldosterone	360.45	12.31	1.63	4	2	-4.24	*J.Pharm.Sci.*, 84:1144-1146
27	androstedione	288.42	10.03	2.75	2	0	-2.91	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
28	aniline	93	10.83	1.08	1	1	-1.21	*I.J.Pharmac.* 129: 33-40
29	atenolol	266.3	12.49	-0.03	4	3	-4.30	*Int.J.Pharm.*, 194: 249-259
30	benzene	78.12	9.19	1.99	0	0	-0.95	*J.Invest.Dermatol.*,85: 522-526
31	benzoic acid	122.1	11.94	1.87	1	1	-2.88	*J.Pharm.Sci.*, 85:249-252

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	Log K_p (cmh^{-1})	Journal
32	benzyl nicotinate	213.24	11.55	2.35	2	0	-1.80	*J.Pharm.Sci.*, 80:54-56
33	b-estradiol	272.4	11.90	3.94	2	2	-2.00	*Pharm.Res.*, 10:1745-1750
34	betamethasone	392.45	12.37	2.02	6	3	-5.70	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
35	bisoprolol	325.5	10.01	1.84	5	2	-3.57	*Int.J.Pharm.*, 173:141-148
36	bisphenol A diglycidyl ether (BADGE)	340.8	10.38	3.84	4	0	-6.32	*Xenobiotica*, 30:469-483
37	boric acid	61.83	44.06	-0.22	3	3	-3.30	*Toxicol.Sci.*, 45: 42-51
38	butyl nicotinate	179.22	10.57	2.11	2	0	-1.78	*J.Pharm.Sci.*, 80: 54-56
39	butyl paraben	194.23	11.45	3.47	2	1	-1.25	*J.Pharm.Sci.*, 96, No. 4, 2007
40	caffeine	194.2	32.83	0.16	4	0	-3.68	*J.Dermatol.*, 115:1-11
41	cannabidiol	314.46	11.11	8.01	2	2	-3.62	*Pharm.Pharmacol.*, 56: 291-297
42	cannabinol	310.46	10.9	7.23	2	1	-3.82	*Pharm.Pharmacol.*, 56: 291-297
43	celiprolol	379.5	11.51	1.93	5	3	-3.23	*Int.J.Pharm.*, 173:141-148
44	chloroxylenol	156.6	11.20	3.25	1	1	-1.23	*J.Pharm.Pharmacol.*,29:677-683
45	chlorpyrifos	350.59	10.10	4.66	1	0	-3.60	*Hum.Exp.Toxicol*,19:104-107
46	cimetidine	252.34	12.86	0.4	6	3	-4.42	*Eur.J.Pharm.Sci.*, 2006
47	clotrimazole	344.85	11.17	6.26	2	0	-2.70	*Int.J.Pharm.*,215:51-56
48	codeine	299.4	12.09	1.28	4	1	-4.31	*Pharmaceut.Res.*, 6:825-832
49	cortexolone	346.47	11.91	3.15	4	2	-4.12	*J.Investig.Dermatol.*, 52:63-70
50	corticosterone	346.5	11.91	1.99	4	2	-4.22	*J.Investig.Dermatol.*, 52:63-70
51	cortisone	360.5	12.1	1.81	5	2	-5.00	*J.Investig.Dermatol.*, 52:63-70
52	coumarin	146.15	11.91	1.51	1	0	-2.04	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
53	DDT	354.49	9.45	6.79	0	0	-2.23	*Toxicol.Vitro*, 8: 1225-1232
54	DEHP	390.57	9.39	8.39	2	0	-5.24	*Environ.Health Perspect.*, 74:223-227
55	deoxyadenosine	251.24	15.49	-0.55	8	3	-3.89	*Eur.J.Pharm.Sci.*, 2006
56	DEP	222.24	10.51	2.65	2	0	-4.94	*Environ.Health Perspect.*, 74:223-227
57	diazinon	304.35	14.98	3.86	2	1	-2.02	*Toxicol.Vitro*, 8:1219-1224
58	dibutyl squarate	226.27	10.58	2.45	4	0	-4.70	*Arch.Dermatol.Res.*, 280:57-60
59	dibutylphthalate	278.35	10.86	5.11	2	0	-5.64	*Environ.Health Perspect.*, 74:223-227

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	Log K_p (cmh^{-1})	Journal
60	dichlofenac	296.16	11.13	4.02	2	2	-3.00	*Int.J.Pharm.*, 170:129-133
61	diethyl squarate	170.16	11.50	4.07	4	0	-3.92	*Arch.Dermatol.Res.*, 280:57-60
62	dimethylformamide	73.1	10.63	-0.93	1	0	-2.02	*Occup.Hyg.*, 1:191-198
63	dodecyl glycidyl ether (C12GE)	242.2	8.41	5.01	2	0	-5.48	*Xenobiotica*, 30:469-483
64	doxycycline HCL	444.44	16.55	-1.36	9	6	-5.32	*Int.Journal of Pharm.*, 190: 155-164
65	estriol	288.4	12.95	2.81	3	3	-4.40	*J.Investig.Dermatol.*, 52: 63-70
66	estrone	270.4	11.55	3.43	2	1	-2.44	*J.Investig.Dermatol.*, 52: 63-70
67	ethanol	46.07	10.92	-0.14	1	1	-3.50	*J.Investig.Dermatol.*, 96: 921-925
68	ethinyl estradiol	296.4	12.04	4	2	1	-4.43	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
69	ethyl nicotinate	151.17	11.06	1.13	2	2	-2.22	*J.Pharm.Sci.*, 80:54-56
70	ethylaniline	121.2	9.73	2.11	1	1	-0.54	*I.J.Pharmac.* 129: 33-40
71	etodolac	287.26	10.86	3.93	3	2	-2.13	*J.Pharm.Sci*ence, 92:3:656-664
72	etorphine	411.55	11.76	3.02	5	2	-2.44	*Pharm.Res.*, 9: 963-965
73	fentanyl	336.5	10.30	3.89	2	0	-2.25	*Pharm.Res.*, 6: 825-832
74	flufenamic acid	281.2	10.96	4.88	5	2	-3.26	*J.Contr.Rel.*, 75:283-295
75	glyphosate	169.10	12.73	-4.47	3	4	-3.34	*Food Chem.Toxicol.*,34:731-735
76	griseofulvin	352.77	10.44	1.92	6	0	-2.71	*Meth. and Find Exp.Clin.Pharmacol.*, 11:643-646
77	hydrocortisone	362.5	12.75	1.61	5	3	-3.80	*J.Contr.Release*, 76:327-335
78	hydromorphone	285.34	10.96	1.6	4	1	-4.82	*Pharm.Res.*, 6: 825-832
79	hydroquinone	110.11	15.18	1.03	2	2	-5.03	*Food Chem.Toxicol.*,35:1009-1016
80	ibuprofen	206.3	10.21	3.79	1	1	-1.44	*Int.J.Pharm.*,170:129-133
81	isosorbide dinitrate (ISDN)	236.14	10.36	0.76	4	0	-2.35	*Eur.J.Pharm.Sci.*, 11:59-68
82	ITF 296	238	12.91	1.61	3	0	-2.45	*Eur.J.Pharm.Sci.*, 11:59-68
83	ketoprofen	254.29	11.75	3.12	2	1	-3.21	*J.Pharm.Sci*ence, 92:3:656-664
84	lidocaine	234.34	8.78	1.66	2	1	-1.97	*Int.J.Pharm.*, 71:167-173
85	lindane	290.83	8.54	4.26	0	0	-5.23	*Hum.Exp.Toxicol.*, 16: 652-657
86	linoleic acid	289.45	9.05	7.51	1	1	-4.97	*J.Pharm.Pharmacol.*, 34:610-611
87	malathion	330.36	10.61	2.29	2	0	-0.69	*Food Chem.Toxicol.*,34:731-735

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	Log K_p (cmh^{-1})	Journal
88	mannitol	182.17	18.63	-3.01	6	6	-4.60	*Toxicol.Vitro*, 8:827-830
89	meperidine	247.4	9.82	3.03	2	0	-2.43	*Pharm.Res.* 6:825-832
90	methanol	32.04	11.68	-0.84	1	1	-2.80	*Int.J.Pharm.*, 18: 299-309
91	methiocarb	225.31	10.92	2.87	1	1	-2.96	*Ann.Occup.Hyg.*,48:697-701
92	methotrexate	454.45	15.05	-1.28	10	5	-3.95	*Int.J.Pharm.*, 25:65-75
93	methyl nicotinate	137.14	11.80	0.64	2	0	-2.47	*J.Pharm.Sci.*,80:54-56
94	methyl paraben	152.15	12.5	2	2	1	-5.23	*J.Pharm.Sci.*, 96, No. 4, 2007
95	methyl parathion	263.21	10.45	2.75	1	0	-4.42	*Occup.Environ.Med.*,54:524-525
96	methyl-4-hydroxy benzoate	152.14	12.50	2	2	1	-2.32	*J.Soc.Cosmet.Chem.*,40:231-242
97	metoprolol	267.4	10.39	1.69	4	2	-3.08	*Int.J.Pharm.*, 194: 249-259
98	morphine	285.3	13.68	0.72	4	2	-5.03	*Pharmaceut.Res.*, 6: 825-832
99	naltrexone (NTX)	341	13.75	1.39	5	2	-2.02	*J.Pharm.Sci.*,91: 2571-2578
100	naproxene	230.3	11.42	3.1	2	1	-2.54	*Int.J.Pharm.*,170:129-133
101	n-hexyl nicotinate	207.27	10.49	3.1	2	0	-1.75	*J.Pharm.Sci.*,80:54-56
102	nicorandil	211.18	14.40	0.43	3	1	-4.30	*Eur.J.Pharm.Sci.*, 11:59-68
103	nicotine	162.3	11.25	1	2	0	-1.99	*Eur.J.Pharm.Sci.*, 11:59-68
104	nicotinic acid	123.11	13.23	0.69	2	1	-4.62	*J.Pharm.Sci.*, 80:104-107
105	nikel	58.7	0	-0.57	0	0	-3.21	*Toxicology Letters* 170 (2007), 49-56
106	nimesulide	308.31	15.25	2.22	3	2	-3.00	*J.Pharm.Sci*ence, 92:3:656-664
107	nizatidine	331.45	12.36	-0.43	5	2	-4.43	*J.Pharm.Sci*ence, 92:3:656-664
108	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	-2.65	*Toxicol.Vitro*, 7:141-148
109	n-nitrosodiethanolamine	134.13	15.67	-1.28	4	2	-2.39	*Food Chem.Toxicol.*,33:315-322
110	n-octanol	130.23	9.45	2.81	1	1	-1.21	*Int.J.Pharm.*, 18:299-309
111	nonane	128.3	7.51	4.76	0	0	-4.38	*Toxicol.Sci.*, 55:247-255
112	NTX-3 heptanoate (HEP-NTX)	453	11.44	3.92	5	1	-3.05	*J.Pharm.Sci.*,91: 2571-2578
113	NTX-3-acetate (ACE-NTX)	383	12.96	1.47	5	1	-2.11	*J.Pharm.Sci.*,91: 2571-2578
114	NTX-3-butyrate (BUT-NTX)	411	11.88	2.45	5	1	-2.89	*J.Pharm.Sci.*,91: 2571-2578
115	NTX-3-hexanoate (HEX-NTX)	439	11.57	2.94	5	1	-2.92	*J.Pharm.Sci.*,91: 2571-2578

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	Log K_p (cmh^{-1})	Journal
116	NTX-3-propionate (PROP-NTX)	397	12.06	1.96	5	1	-2.60	*J.Pharm.Sci.*,91: 2571-2578
117	NTX-3-valerate (VAL-NTX)	425	11.72	2.45	5	1	-3.15	*J.Pharm.Sci.*,91: 2571-2578
118	o-cresyl glycidyl ether (oCGE)	164.2	10.38	2.16	2	0	-4.03	*Xenobiotica*,30:469-483
119	oxprenolol	265.4	10.52	1.83	4	2	-2.81	*Int.J.Pharm.*, 194: 249-259
120	paraquat	257.16	10.45	-2.71	0	0	-5.06	*J.Investig.Dermatol.*, 96:921-925
121	parathion	291.26	10.76	3.73	1	0	-3.72	*Toxicol.Appl.Pharmacol.*, 168:149-152
122	phenol	94.11	12.33	1.51	1	1	-2.09	*J.Pharm.Pharmacol.*, 29:677-683
123	pirimicarb	238.29	11.05	1.4	4	0	-2.57	*Ann.Occup.Hyg.*,48:697-701
124	prednisolone	360.44	12.96	1.49	5	3	-4.63	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
125	prednisone	358.44	12.71	1.46	5	2	-4.61	*Biol.Pharm.Bull.*, 29 (11) 2270-2273
126	pregnenolone	316.5	10.36	3.89	2	1	-2.82	*J.Investig.Dermatol.*, 52:63-70
127	prochloraz	376.7	10.69	4.13	3	0	-3.15	*Ann.Occup.Hyg.*,48:697-701
128	progesterone	314.5	10.05	3.67	2	0	-1.52	J.Pharm. Sci., 84:1144-1146
129	propoxur	209.25	10.31	1.9	2	1	-3.05	*Toxicol.Sci.*, 58:15-22
130	propranolol	295.3	11.13	2.6	3	2	-2.75	*Int.J.Pharm.*, 194: 249-259
131	ranitidine	314.1	11.41	0.29	5	2	-4.05	*J.Pharm.Sc*ience, 92:3:656-664
132	resorcinol	110.11	15.18	1.03	2	2	-3.62	*J.Pharm.Pharmacol.*,29:677-683
133	salicylic acid	138.1	14.39	2.24	2	2	-1.89	*Eur.J.Pharm.Sci.*, 11:59-68
134	squaric acid	114.06	20.47	-0.44	4	2	-5.12	*Arch.Dermatol.Res.*,280:57-60
135	sufentanil	386.6	10.47	3.62	3	0	-1.92	*Pharm.Res*,6:825-832
136	terbinafine	291.4	9.33	5.81	1	0	-3.00	*Int.J.Pharm.*,215:51-56
137	testosterone	288.4	10.66	3.27	2	1	-2.17	*J.Dermatol.*,115:1-11
138	theophylline	180.17	14.05	-0.39	4	1	-3.36	*J.Soc.Cosmet.Chem.*, 40:231-242
139	thymol	150.2	10.81	3.52	1	1	-1.28	*J.Pharm.Pharmacol.*, 29:677-683
140	triclosan	289.55	10.02	2.47	2	1	-4.47	*Int.J.Pharm.*,235:229-236
141	water	18.02	26.68	-1.38	1	1	-3.15	*Toxicol.Vitro*, 8:827-830
142	Δ-tetrahydrocannabinol (THC)	314.46	9.75	7.6	2	1	-4.55	*Pharm.Pharmacol.*, 56: 291-297
143	captopril	303.40	25.23	0.84	4.00	1	-2.83	*J.Pharm.Pharmacology*, 58: 167-177

No	Name	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	Log K_p (cmh^{-1})	Journal
144	methyl ester	245.29	23.04	2.90	4	0	-2.44	*J.Pharm.Pharmacology*, 58: 167-177
145	ethyl ester	273.29	22.63	3.39	4	0	-2.09	*J.Pharm.Pharmacology*, 58: 167-177
146	propyl ester	287.29	22.29	3.89	4	0	-1.91	*J.Pharm.Pharmacology*, 58: 167-177
147	butyl ester	301.29	21.98	4.38	4	0	-1.97	*J.Pharm.Pharmacology*, 58: 167-177
148	pentyl ester	136.10	21.71	4.87	4	0	-2.97	*J.Pharm.Pharmacology*, 58: 167-177
149	hexyl ester	354.30	21.47	5.36	4	0	-2.91	*J.Pharm.Pharmacology*, 58: 167-177

Group A20

Type of skin: human Site: all types All temperatures

Ionisation effect

No	Name	Log D	SP	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	C (mg/ml)	C (1M)	pKa	Ka	CKA	√(cKA)	pH	Delta
1	2,4 dimethylamine	4.50	9.52	3	2	0.000945	-3.02	9.73	2588.91	10.73	1.86E-11	4.82E-08	0.000219563	3.66	-3.65
2	3-nitrophenol	4.69	13.02	2	1	0.00564	-2.25	5	695.5	8.4	3.98E-09	2.77E-06	0.001663982	2.78	-2.78
3	atenolol	3.17	12.49	4	3	0.00005	-4.30	4.8	1278.24	9.5	3.16E-10	4.04E-07	0.000635779	3.20	-3.20
4	b-estradiol	7.00	11.90	2	2	0.01	-2.00	10	2724	10.46	3.47E-11	9.45E-08	0.000307329	1.34	-3.06
5	bisoprolol	3.94	10.01	5	2	0.00027	-3.57	5	1627.5	9.5	3.16E-10	5.15E-07	0.000717399	0.34	-2.10
6	celiprolol	4.23	11.51	5	3	0.00059	-3.23	5	1897.5	9.7	1.99E-10	3.79E-07	0.000615306	3.21	-2.30
7	clotrimazole	6.28	11.17	2	0	0.002	-2.70	0.01	3.45	6.12	7.59E-07	2.62E-06	0.001617391	2.79	-0.02
8	codeine	2.32	12.09	4	1	0.000049	-4.31	2.14	640.72	8.4	3.98E-09	2.55E-06	0.001597102	2.80	-1.04
9	estriol	5.79	12.95	3	3	0.00004	-4.40	0.002	0.58	10.38	4.17E-11	2.40E-11	4.90E-06	5.31	-2.98
10	estrone	6.37	11.55	2	1	0.0036	-2.44	0.00068	0.18	10.34	4.57E-11	8.40E-12	2.90E-06	5.54	-2.94
11	hydrocortisone	6.69	12.75	5	3	0.0023	-2.64	1.2	435	12.48	3.31E-13	1.44E-10	1.20E-05	4.92	-5.08
12	meperidine	4.28	9.82	2	0	0.0037	-2.43	6.55	1620.47	8.63	2.34E-09	3.80E-06	0.001949039	2.71	-1.25
13	methyl parathion	4.36	10.45	1	0	0.000038	-4.42	1.11	290.85	9	0.000000001	2.91E-07	0.000539302	3.27	-1.61
14	metoprolol	3.99	10.39	4	2	0.00083	-3.08	4.47	1195.28	9.7	1.99E-10	2.38E-07	0.000488354	3.31	-2.30
15	morphine	1.34	13.68	4	2	0.0000093	-5.03	0.72	205.42	7.9	1.26E-08	2.59E-06	0.001608115	2.79	-0.62
16	oxprenolol	3.93	10.52	4	2	0.00154	-2.81	4.42	1173.1	9.5	3.16E-10	3.71E-07	0.000609062	3.22	-2.10
17	propoxur	6.78	10.31	2	1	0.000885	-3.05	1.92	401.76	12.28	5.25E-13	2.11E-10	1.45E-05	4.84	-4.88
18	propranolol	4.70	11.13	3	2	0.00178	-2.75	5	1476.5	9.5	3.16E-10	4.67E-07	0.000683308	3.17	-2.10

No	Name	Log D	SP	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	C (mg/ml)	C (1M)	pKa	Ka	CKA	√(cKA)	pH	Delta
19	resorcinol	3.44	15.18	2	2	0.00024	-3.62	100	11011	9.81	1.55E-10	1.71E-06	0.00130591	2.88	-2.41
20	sufentanil	4.33	10.47	3	0	0.012	-1.92	0.034	13.14	8.01	9.77E-09	1.3E-07	0.000358402	3.45	-0.71

Group A21

Type of skin: human Site: all types All temperatures Time Any analytical tool Vehicle: any Receptor fluid any

Static / flow through-duplicates were eliminated

No	Name	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})
1	1,6-hexanediol diglycidyl ether (HDDGE)	9.36	0.84	4	0	0.000136	-3.87
2	adenosine	15.97	-1.05	9	4	0.000133	-3.88
3	bisphenol A diglycidyl ether (BADGE)	10.38	3.84	4	0	4.80E-07	-6.32
4	boric acid	44.06	-0.22	3	3	0.0005	-3.30
5	cannabidiol	11.11	8.01	2	2	0.00024	-3.62
6	cannabinol	10.9	7.23	2	1	0.00015	-3.82
7	chlorpyrifos	10.10	4.66	1	0	0.00011	-3.96
8	cimetidine	12.86	0.4	6	3	0.000038	-4.42
9	codeine	12.09	1.28	4	1	0.000049	-4.31
10	DDT	9.45	6.79	0	0	0.00594	-2.23
11	deoxyadenosine	15.49	-0.55	8	3	0.000129	-3.89
12	diazinon	14.98	3.86	2	1	0.0095	-2.02
13	dichlofenac	11.13	4.02	2	2	0.001	-3.00
14	dodecyl glycidyl ether (C12GE)	8.41	5.01	2	0	0.00000331	-5.48
15	doxycycline HCL	16.55	-1.36	9	6	0.00000477	-5.32
16	etorphine	11.76	3.02	5	2	0.0036	-2.44
17	glyphosate	12.73	-4.47	3	4	0.000459	-3.34
18	griseofulvin	10.44	1.92	6	0	0.00194	-2.71
19	hydromorphone	10.96	1.6	4	1	0.000015	-4.82
20	ibuprofen	10.21	3.79	1	1	0.0363	-1.44
21	isosorbide dinitrate (ISDN)	10.36	0.76	4	0	0.00449	-2.35

No	Name	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})
22	lindane	8.54	4.26	0	0	0.0000059	-5.23
23	malathion	10.61	2.29	2	0	0.203	-0.69
24	methiocarb	10.92	2.87	1	1	0.0011	-2.96
25	methyl nicotinate	11.80	0.64	2	0	0.00389	-2.41
26	methyl parathion	10.45	2.75	1	0	0.000013	-4.87
27	methyl-4-hydroxy benzoate	12.50	2	2	1	0.00478	-2.32
28	morphine	13.68	0.72	4	2	0.0000093	-5.03
29	naproxene	11.42	3.1	2	1	0.00288	-2.54
30	nicotine	11.25	1	2	0	0.0103	-1.99
31	o-cresyl glycidyl ether (oCGE)	10.38	2.16	2	0	9.30E-05	-4.03
32	pirimicarb	11.05	1.4	4	0	0.0027	-2.57
33	prochloraz	10.69	4.13	3	0	0.0007	-3.15
34	salicylic acid	14.39	2.24	2	2	0.0131	-1.89
35	theophylline	14.05	-0.39	4	1	0.000432	-3.36
36	Δ-tetrahydrocannabinol (THC)	9.75	7.6	2	1	0.000028	-4.55

Group A22

Type of skin: human | Site: all types | All temperatures | Time | Any analytical tool | Vehicle: any

low lipophilicity | Receptor fluid: any

No	Name	MW	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p
1	glyphosate	169.10	-4.47	3	4	0.000459	-3.34
2	mannitol	182.17	-3.01	6	6	0.000025	-4.60
3	methanol	32.04	-0.63	1	1	0.0016	-2.80
4	deoxyadenosine	251.24	-0.55	8	3	0.000129	-3.89
5	2-ethoxyethanol	90.12	-0.42	2	1	0.000842	-3.07
6	atenolol	266.3	-0.03	4	3	0.00005	-4.30
7	caffeine	194.2	0.16	4	0	0.00021	-3.68
8	cimetidine	252.34	0.4	6	3	0.000038	-4.42
9	nicorandil	211.18	0.43	3	1	0.00005	-4.30
10	nicotinic acid	123.11	0.69	2	1	0.000024	-4.62
11	morphine	285.3	0.72	4	2	0.0000093	-5.03
12	2,4 dimethylamine	266.13	0.84	3	2	0.000945	-3.02

Group A23

Type of skin: human | Site: all types | All temperatures | Time | Any analytical tool | Vehicle: any

medium lipophilicity | Receptor fluid: any

No	Name	MW	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p
1	nicotine	162.3	1	2	0	0.0103	-1.99
2	prednisone	358.44	1.46	5	2	0.0000246	-4.61
3	2-phenylethanol	122.2	1.57	1	1	0.031	-1.51
4	lidocaine	234.34	1.66	2	1	0.0106	-1.97
5	propoxur	209.25	1.9	2	1	0.000885	-3.05
6	benzene	78.12	1.99	0	0	0.111	-0.95
7	corticosterone	346.5	1.99	4	2	0.00006	-4.22
8	betamethasone	392.45	2.02	6	3	0.000002	-5.70
9	ethylaniline	121.2	2.11	1	1	0.288	-0.54
10	salicylic acid	138.1	2.24	2	2	0.0131	-1.89
11	estriol	288.4	2.81	3	3	0.00004	-4.40
12	NTX-3-hexanoate (HEX-NTX)	439	2.94	5	1	0.0012	-2.92

Group A24

Type of skin: human high lipophilicity | Site: all types | All temperatures | Receptor fluid: any | Time | Any analytical tool | Vehicle: any

No	Name	MW	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p
1	etorphine	411.55	3.02	5	2	0.0036	-2.44
2	n-hexyl nicotinate	207.27	3.1	2	0	0.0179	-1.75
3	2-phenylphenol	170.21	3.28	1	1	0.0183	-1.74
4	estrone	270.4	3.43	2	1	0.0036	-2.44
5	ibuprofen	206.3	3.79	1	1	0.0363	-1.44
6	pregnenolone	316.5	3.89	2	1	0.0015	-2.82
7	b-estradiol	272.4	3.94	2	2	0.01	-2.00
8	prochloraz	376.7	4.13	3	0	0.0007	-3.15
9	flufenamic acid	281.2	4.88	5	2	0.0005499	-3.26
10	linoleic acid	289.45	7.51	1	1	0.0000106	-4.97
11	cannabidiol	314.46	8.01	2	2	0.00024	-3.62

Appendix 6. Rat skin dataset

Group B1

Type of skin: rat | Site: dorsal / abdomen | 32 °C at the surface of the skin | Timeof24-48h | HPLC / GC / radiolabelled | Vehicle: water | propylene glycol | Receptor fluid | normal saline | HEPES-buffered Hanks´ balanced salt solution

Cell type: flow through cells / static | 37 °C in WB | physiological buffer | ethanol, methanol | MEM

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	dodecyl decaethoxylate	482.9	4.33	not calc.	not calc.	not calc.	0.0000049	-5.31	methanol	dermatomed 0.24 mm	dorsal	flow-through	MEM, penicillin & streptomycin	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
2	dodecyl monoethoxylate	230.4	4.5	9.16	2	1	0.00000032	-6.49	methanol	dermatomed 0.24 mm	dorsal	flow-through	MEM, penicillin & streptomycin	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
3	2-phenoxyethanol	138.17	1.1	11.49	2	1	1.76E-05	-4.75	methanol	dermatom.0.24 mm	dorsal	flow-through	MEM & penicillin / streptomycin + CO2	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
4	2-phenoxyethanol	138.17	1.1	11.49	2	1	0.001764	-2.75	methanol	dermatom.0.24 mm	dorsal	flow-through	MEM & penicillin / streptomycin + CO2	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016
5	2-phenoxyethanol	138.17	1.1	11.49	2	1	0.00272	-2.57	methanol	dermatom.0.24 mm	dorsal	static	50% aq. ethanol	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016
6	2-phenoxyethanol	138.17	1.1	11.49	2	1	2.72E-05	-4.57	methanol	dermatom.0.24 mm	dorsal	static	aq. ethanol	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
7	2-phenoxyethanol	138.17	1.1	11.49	2	1	0.00735	-2.13	methanol	dermatom.0.24 mm	dorsal	static	50% aq. ethanol	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016
8	theophylline	180.17	-0.39	14.05	4	1	0.00923	-2.03	1-propanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242
9	theophylline	180.17	-0.39	14.05	4	1	0.0109	-1.96	ethanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242
10	theophylline	180.17	-0.39	14.05	4	1	0.0139	-1.86	methanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242
11	theophylline	180.17	-0.39	14.05	4	1	0.0022	-2.66	water	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242
12	dodecyl decaethoxylate	482.9	4.33	not calc.			0.000429	-3.37	methanol	dermatomed 0.24 mm	dorsal	static	aq. ethanol	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
13	dodecyl monoethoxylate	230.4	4.5	9.16	2	1	0.00546	-2.26	methanol	dermatomed 0.24 mm	dorsal	static	aq. ethanol	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65

Group B2

Type of skin: rat | Site: all sites | 32 °C at the surface of the skin | Timeof24-48h | HPLC / GC / radiolabelled | Vehicle: water | propylene glycol | Receptor fluid | normal saline | HEPES-buffered Hanks´ balanced salt solution

Cell type: flow through cells | 37 °C in WB | physiological buffer | ethanol, methanol | MEM

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	alizapride	339.9	1.8	12.06	6	2	0.0057	-2.24	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
2	benzyl acetate	150.18	2.08	10.10	1	0	0.00027	-3.57	none	full-thickness	dorsal	flow-through	0.9% saline	32(skin)	48	radiolabelled (14C)	*Food Chem.Toxicol..*, 28: 443-447
3	benzyl acetate	150.18	2.08	10.10	1	0	0.000058	-4.24	50% aq. ethanol	full-thickness	dorsal	flow-through	0.9% saline	32(skin)	48	radiolabelled (14C)	*Food Chem.Toxicol..*, 28: 443-447
4	bisphenol A diglycidyl ether (BADGE)	340.8	3.84	10.38	4	0	5.50E-06	-5.26	acetone	dermatomed skin	dorsal	flow-through	HBSS, HEPES buffer BSA& gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*,30:469-483
5	bromopride	344.26	1.94	10.74	4	2	0.0078	-2.11	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
6	caffeine	194.2	0.16	32.83	4	0	0.001025	-2.99	50% aq. ethanol	full-thickness	not available	flow-through	saline	37	24	radiolabelled (14C)	*Toxicology*, 178:65-66
7	clebopride	373.9	3.21	11.47	4	2	0.0074	-2.13	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
8	DDT	354.49	6.79	9.45	0	0	0.0068	-2.17	acetone	dermatomed 0.5mm	back	flow-through	Hanks HEPES buffered medium, 4% BSA & gentamycin	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8:1225-1232
9	dodecyl decaethoxylate	482.9	4.33	not calc.			0.0000049	-5.31	methanol	dermatomed 0.24 mm	dorsal	flow-through	MEM, penicillin & streptomycin	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
10	dodecyl glycidyl ether (C12GE)	242.2	5.01	8.41	2	0	0.000029	-4.54	acetone	dermatomed skin	dorsal	flow-through	HEPES, HBSS & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
11	dodecyl monoethoxylate	230.4	4.5	9.16	2	1	0.00000032	-6.49	methanol	dermatomed 0.24 mm	dorsal	flow-through	MEM, penicillin & streptomycin	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
12	domperidone	425.92	3.35	12.48	3	2	0.0028	-2.55	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
13	felodipine	384.3	3.86	10.43	3	1	0.004	-2.40	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
14	fenoxapropethyl	361.78	4.95	11.06	5	0	0.00071	-3.15	acetone	dermatom. 0.6 mm	back	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 6:53-59
15	fenoxapropethyl	361.78	4.95	11.06	5	0	0.00035	-3.46	acetone	dermatom. 0.9 mm	back	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 6:53-59
16	fenoxapropethyl	361.78	4.95	11.06	5	0	0.00035	-3.46	acetone	dermatom. 0.8 mm	back	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 6:53-59
17	haloperidol	375.9	4.22	10.78	4	1	0.02	-1.70	lactic acid & antibacterial antimycotic solution	full-thickness	abdomen	flow-through	0.03% v/v lactic acid solution	37	48	RP HPLC	*Int.J.Pharm.*, 212: 247-255
18	1,6-hexanediol diglycidyl ether (HDDGE)	230.2	0.84	9.36	4	0	0.000402	-3.40	acetone	dermatomed	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
19	metochloropramide	354.3	1.69	11.13	4	2	0.0091	-2.04	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
20	metopimazine	445.61	2.42	13.55	3	1	0.0051	-2.29	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
21	N-N-diethyl m-toluamide	191.28	2.26	10.70	1	0	0.00168	-2.77	acetone	dermat.0.5mm	back	flow-through	sterile Ringer's solution, Trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*,7:141-148
22	nicardipine	479.54	3.9	10.87	5	1	0.0049	-2.31	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
23	nifedipine	346.3	4.04	10.92	4	0	0.0017	-2.77	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
24	nimodipine	418.4	3.13	10.50	3	1	0.0026	-2.59	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
25	nitrendipine	360.4	2.99	11.44	5	1	0.0039	-2.41	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
26	2-phenoxyethanol	138.17	1.1	11.49	2	1	1.76E-05	-4.75	methanol	dermatom.0.24 mm	dorsal	flow-through	MEM & penicillin / streptomycin + CO2	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
27	2-phenoxyethanol	138.17	1.1	11.49	2	1	0.001764	-2.75	methanol	dermatom.0.24 mm	dorsal	flow-through	MEM & penicillin / streptomycin + CO2	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016
28	scopolamine	303.4	0.39	11.53	4	1	0.0041	-2.39	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
29	theophylline	180.17	-0.39	14.05	4	1	0.00923	-2.03	1-propanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242
30	theophylline	180.17	-0.39	14.05	4	1	0.0109	-1.96	ethanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242
31	theophylline	180.17	-0.39	14.05	4	1	0.0139	-1.86	methanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242
32	theophylline	180.17	-0.39	14.05	4	1	0.0022	-2.66	water	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242

Group B3

Type of skin: rat | Site: all sites | 32 °C at the surface of the skin | Timeof24-48h | HPLC / radiolabelled | GC / | Vehicle: water | propylene glycol | Receptor fluid | normal saline | HEPES-buffered Hanks´ balanced salt solution

Cell type: static | 37 °C in WB | physiological buffer | ethanol, methanol | MEM

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	butyl salicylate	194.23	4.08	11.45	2	1	0.00002	-4.7	dimethyl isosorbide & 2-propanol	full-thickness	not available	static	isotonic phosphate buffer	32 (skin)	48	HPLC	*Eur.J.Pharm.Sci.*, 17:95-104
2	dodecyl decaethoxylate	482.9	4.33	not calc.	not calc.	not calc.	0.000429	-3.37	methanol	dermatomed 0.24 mm	dorsal	static	aq. ethanol	37	24	radiolabelled (14C)	*Toxicol.Vitro,* 12:57-65
3	dodecyl monoethoxylate	230.4	4.5	9.16	2	1	0.00546	-2.26	methanol	dermatomed 0.24 mm	dorsal	static	aq. ethanol	37	24	radiolabelled (14C)	*Toxicol.Vitro,* 12:57-65
4	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.00000396	-5.4	40% propylene glycol	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
5	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.00001322	-4.88	propylene glycol & dodecylazacycloheptan-2-one	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
6	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.00000542	-5.27	40% propylene glycol & 5% dimethylsulphoxide	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
7	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.000075	-4.12	40% propylene glycol & 2.25% sodium lauryl sulphate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
8	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.0000099	-5.00	40% propylene glycol & 1% dodecyl-L-pyroglutamate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
9	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.00002	-4.70	40% propylene glycol & 10% N-methyl-2-pyrrolidone	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
10	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.0000197	-4.70	40% propylene glycol & 12% N-methyl-2-pyrrolidone	full-thickness	abdomen	static	saline	37	26	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
11	lorazepam	321.16	2.41	12.91	3	2	0.000051	-4.29	50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
12	lorazepam	321.16	2.41	12.91	3	2	0.0001146	-3.94	0.5% tween 80 & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
13	lorazepam	321.16	2.41	12.91	3	2	0.000078	-4.11	5% tween 80 & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
14	lorazepam	321.16	2.41	12.91	3	2	0.0001994	-3.70	0.5% benzalkonium Cl & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
15	lorazepam	321.16	2.41	12.91	3	2	0.0003591	-3.44	5% benzalkonium Cl & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
16	lorazepam	321.16	2.41	12.91	3	2	0.0001501	-3.82	0.5% SLS & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
17	lorazepam	321.16	2.41	12.91	3	2	0.0005662	-3.25	5% SLS & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
18	nicorandil	211.18	0.43	14.40	3	1	0.000727	-3.14	water	full-thickness	abdomen	static	saline	37	32	HPLC	*J.Pharm.Pharmacol.*, 41:379-383
19	2-phenoxyethanol	138.17	1.1	11.49	2	1	0.00272	-2.57	methanol	dermatom.0.24 mm	dorsal	static	50% aq. ethanol	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016
20	2-phenoxyethanol	138.17	1.1	11.49	2	1	2.72E -05	-4.57	methanol	dermatom.0.24 mm	dorsal	static	aq. ethanol	37	24	radiolabelled (14C)	*Toxicol.Vitro,* 12:57-65
21	2-phenoxyethanol	138.17	1.1	11.49	2	1	0.00735	-2.13	methanol	dermatom.0.24 mm	dorsal	static	50% aq. ethanol	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016
22	salicylamide	137.14	1.03	16.60	2	2	0.000017	-4.77	dimethyl isosoride & 2-propanol	full-thickness	not available	static	isotonic phosphate buffer	32 (skin)	48	HPLC	*Eur.J.Pharm.Sci.*., 17:95-104
23	salicylic acid	138.1	2.24	14.39	2	2	0.000024	-4.62	dimethyl isosoride & 2-propanol	full-thickness	not available	static	isotonic phosphate buffer	32 (skin)	48	HPLC	*Eur.J.Pharm.Sci.*., 17:95-104

Group B4

Type of skin: rat | Site: all sites | 32 °C at the surface of the skin | Timeof24-48h | HPLC / radiolabelled | GC / | Vehicle: water | propylene glycol | Receptor fluid | normal saline | HEPES-buffered Hanks´ balanced salt solution

Cell type: static / flow-through | 37 °C in WB | physiological buffer | ethanol, methanol | MEM

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	alizapride	339.9	1.8	12.06	6	2	0.0057	-2.24	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
2	benzyl acetate	150.18	2.08	10.10	1	0	0.00027	-3.57	none	full-thickness	dorsal	flow-through	0.9% saline	32(skin)	48	radiolabelled (14C)	*Food Chem.Toxicol..*, 28: 443-447
3	benzyl acetate	150.18	2.08	10.10	1	0	0.000058	-4.24	50% aq. ethanol	full-thickness	dorsal	flow-through	0.9% saline	32(skin)	48	radiolabelled (14C)	*Food Chem.Toxicol..*, 28: 443-447
4	bisphenol A diglycidyl ether (BADGE)	340.8	3.84	10.38	4	0	5.50E-06	-5.26	acetone	dermatomed skin	dorsal	flow-through	HBSS, HEPES buffer BSA& gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*,30:469-483
5	bromopride	344.26	1.94	10.74	4	2	0.0078	-2.11	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
6	butyl salicylate	194.23	4.08	11.45	2	1	0.00002	-4.7	dimethyl isosorbide & 2-propanol	full-thickness	not available	static	isotonic phosphate buffer	32 (skin)	48	HPLC	*Eur.J.Pharm.Sci.*, 17:95-104
7	caffeine	194.2	0.16	32.83	4	0	0.001025	-2.99	50% aq. ethanol	full-thickness	not available	flow-through	saline	37	24	radiolabelled (14C)	*Toxicology*, 178:65-66
8	clebopride	373.9	3.21	11.47	4	2	0.0074	-2.13	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
9	DDT	354.49	6.79	9.45	0	0	0.0068	-2.17	acetone	dermatomed 0.5mm	back	flow-through	Hanks HEPES buffered medium, 4% BSA & gentamycin	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8:1225-1232
10	dodecyl decaethoxylate	482.9	4.33	not calc.	not calc.	not calc.	0.000429	-3.37	methanol	dermatomed 0.24 mm	dorsal	static	aq. ethanol	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
11	dodecyl decaethoxylate	482.9	4.33	not calc.	not calc.	not calc.	0.0000049	-5.31	methanol	dermatomed 0.24 mm	dorsal	flow-through	MEM, penicillin & streptomycin	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
12	dodecyl glycidyl ether (C12GE)	242.2	5.01	8.41	2	0	0.000029	-4.54	acetone	dermatomed skin	dorsal	flow-through	HEPES, HBSS & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
13	dodecyl monoethoxylate	230.4	4.5	9.16	2	1	0.00546	-2.26	methanol	dermatomed 0.24 mm	dorsal	static	aq. ethanol	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
14	dodecyl monoethoxylate	230.4	4.5	9.16	2	1	0.00000032	-6.49	methanol	dermatomed 0.24 mm	dorsal	flow-through	MEM, penicillin & streptomycin	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
15	domperidone	425.92	3.35	12.48	3	2	0.0028	-2.55	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
16	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.00000396	-5.4	40% propylene glycol	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
17	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.00001322	-4.88	propylene glycol & dodecylazacycloheptan-2-one	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
18	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.00000542	-5.27	40% propylene glycol & 5% dimethylsulphoxide	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
19	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.000075	-4.12	40% propylene glycol & 2.25% sodium lauryl sulphate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
20	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.0000099	-5.00	40% propylene glycol & 1% dodecyl-L-pyroglutamate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
21	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.00002	-4.70	40% propylene glycol & 10% N-methyl-2-pyrrolidone	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
22	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.0000197	-4.70	40% propylene glycol & 12% N-methyl-2-pyrrolidone	full-thickness	abdomen	static	saline	37	26	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
23	felodipine	384.3	3.86	10.43	3	1	0.004	-2.40	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
24	fenoxapropethyl	361.78	4.95	11.06	5	0	0.00071	-3.15	acetone	dermatom. 0.6 mm	back	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 6:53-59
25	fenoxapropethyl	361.78	4.95	11.06	5	0	0.00035	-3.46	acetone	dermatom. 0.9 mm	back	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 6:53-59

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
26	fenoxapropethyl	361.78	4.95	11.06	5	0	0.00035	-3.46	acetone	dermatom. 0.8 mm	back	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 6:53-59
27	haloperidol	375.9	4.22	10.78	4	1	0.02	-1.70	lactic acid & antibacterial antimycotic solution	full-thickness	abdomen	flow-through	0.03% v/v lactic acid solution	37	48	RP HPLC	*Int.J.Pharm.*, 212: 247-255
28	1,6-hexanediol diglycidyl ether (HDDGE)	230.2	0.84	9.36	4	0	0.000402	-3.40	acetone	dermatomed	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
29	lorazepam	321.16	2.41	12.91	3	2	0.000051	-4.29	50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
30	lorazepam	321.16	2.41	12.91	3	2	0.0001146	-3.94	0.5% tween 80 & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
31	lorazepam	321.16	2.41	12.91	3	2	0.000078	-4.11	5% tween 80 & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
32	lorazepam	321.16	2.41	12.91	3	2	0.0001994	-3.70	0.5% benzalkonium Cl & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
33	lorazepam	321.16	2.41	12.91	3	2	0.0003591	-3.44	5% benzalkonium Cl & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
34	lorazepam	321.16	2.41	12.91	3	2	0.0001501	-3.82	0.5% SLS & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
35	lorazepam	321.16	2.41	12.91	3	2	0.0005662	-3.25	5% SLS & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
36	metochloropramide	354.3	1.69	11.13	4	2	0.0091	-2.04	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
37	metopimazine	445.61	2.42	13.55	3	1	0.0051	-2.29	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
38	N-N-diethyl m-toluamide	191.28	2.26	10.70	1	0	0.00168	-2.77	acetone	dermat.0.5mm	back	flow-through	sterile Ringer's solution, Trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*,7:141-148
39	nicardipine	479.54	3.9	10.87	5	1	0.0049	-2.31	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
40	nicorandil	211.18	0.43	14.40	3	1	0.000727	-3.14	water	full-thickness	abdomen	static	saline	37	32	HPLC	*J.Pharm.Pharmacol.*, 41:379-383
41	nifedipine	346.3	4.04	10.92	4	0	0.0017	-2.77	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
42	nimodipine	418.4	3.13	10.50	3	1	0.0026	-2.59	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
43	nitrendipine	360.4	2.99	11.44	5	1	0.0039	-2.41	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
44	2-phenoxyethanol	138.17	1.1	11.49	2	1	0.00272	-2.57	methanol	dermatom.0.24 mm	dorsal	static	50& aq. ethanol	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016
45	2-phenoxyethanol	138.17	1.1	11.49	2	1	2.72E -05	-4.57	methanol	dermatom.0.24 mm	dorsal	static	aq. ethanol	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
46	2-phenoxyethanol	138.17	1.1	11.49	2	1	1.76E-05	-4.75	methanol	dermatom.0.24 mm	dorsal	flow-through	MEM & penicillin / streptomycin + CO2	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
47	2-phenoxyethanol	138.17	1.1	11.49	2	1	0.001764	-2.75	methanol	dermatom.0.24 mm	dorsal	flow-through	MEM & penicillin / streptomycin + CO2	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016
48	2-phenoxyethanol	138.17	1.1	11.49	2	1	0.00735	-2.13	methanol	dermatom.0.24 mm	dorsal	static	50% aq. ethanol	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016
49	salicylamide	137.14	1.03	16.60	2	2	0.000017	-4.77	dimethyl isosoride & 2-propanol	full-thickness	not available	static	isotonic phosphate buffer	32 (skin)	48	HPLC	*Eur.J.Pharm.Sci.*., 17:95-104
50	salicylic acid	138.1	2.24	14.39	2	2	0.000024	-4.62	dimethyl isosoride & 2-propanol	full-thickness	not available	static	isotonic phosphate buffer	32 (skin)	48	HPLC	*Eur.J.Pharm.Sci.*., 17:95-104
51	scopolamine	303.4	0.39	11.53	4	1	0.0041	-2.39	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
52	theophylline	180.17	-0.39	14.05	4	1	0.00923	-2.03	1-propanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242
53	theophylline	180.17	-0.39	14.05	4	1	0.0109	-1.96	ethanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
54	theophylline	180.17	-0.39	14.05	4	1	0.0139	-1.86	methanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242
55	theophylline	180.17	-0.39	14.05	4	1	0.0022	-2.66	water	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242

Group B5

Type of skin: rat Site: all sites All temperatures Time HPLC / GC / radiolabelled Vehicle: any Receptor fluid any

Cell type: static / flow-through

No	Name	MW	Log P KOWWIN	SP (cal/cm^3) 1/2	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Reference
1	alizapride	339.9	1.8	12.06	6	2	0.0057	-2.24	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
2	aminopyrene	231	0.6	10.7	3	0	0.033	-1.48	IPM	full-thickness	not available	static	ethanol	32	8	HPLC	*Int.J.Pharm.*, 262-13-22
3	aniline	93	1.08	10.83	1	1	0.067	-1.17	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100:1-7
4	benzoic acid	122.1	1.87	11.94	1	1	0.0286	-1.54	ethanol	isol. epidermis	back	flow-through	50& aq. ethanol	31.5 (skin)	30	radiolabelled (14C)	*Toxicol.Vitro*, 12:47-55
5	benzoic acid	122.1	1.87	11.94	1	1	0.00952	-2.02	ethanol	isol. epidermis	back	flow-through	PBS	31.5 (skin)	30	radiolabelled (14C)	*Toxicol.Vitro*, 12:47-55
6	benzoic acid	122.1	1.87	11.94	1	1	0.00035	-3.46	petrolatum	full-thickness	back	static	saline & thimerosol	32	not available	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.*,62:474-480
7	benzoic acid	122.1	1.87	11.94	1	1	0.00029	-3.54	petrolatum	full-thickness	abdomen	static	saline & thimerosol	32	not available	radiolabelled (14C)	*J.Soc.Cosmet.Chem.*,34:127-135
8	benzyl acetate	150.18	2.08	10.10	1	0	0.00027	-3.57	none	full-thickness	dorsal	flow-through	0.9% saline	32(skin)	48	radiolabelled (14C)	*Food Chem.Toxicol..*, 28: 443-447
9	benzyl acetate	150.18	2.08	10.10	1	0	0.000058	-4.24	50% aq. ethanol	full-thickness	dorsal	flow-through	0.9% saline	32(skin)	48	radiolabelled (14C)	*Food Chem.Toxicol..*, 28: 443-447
10	bisphenol A diglycidyl ether (BADGE)	340.8	3.84	10.38	4	0	5.50E-06	-5.26	acetone	dermatomed skin	dorsal	flow-through	HBSS, HEPES buffer BSA& gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*,30:469-483
11	bromopride	344.26	1.94	10.74	4	2	0.0078	-2.11	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
12	bufexamac	223.3	1.98	12.43	3	2	0.271	-0.57	IPM	full-thickness	not available	static	ethanol	32	8	HPLC	*Int.J.Pharm.*, 262-13-22
13	4-n-butylaniline	149	3.1	9.51	1	1	0.23	-0.64	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100:1-7
14	butyl salicylate	194.23	4.08	11.45	2	1	0.00002	-4.7	dimethyl isosorbide & 2-propanol	full-thickness	not available	static	isotonic phosphate buffer	32 (skin)	48	HPLC	*Eur.J.Pharm.Sci.*, 17:95-104
15	caffeine	194.2	0.16	32.83	4	0	0.00031	-3.51	petrolatum	full-thickness	back	static	saline & thimerosol	32	not available	radiolabelled (14C)	*Toxicol.Appl.Pharmacol*,62: 474-480
16	caffeine	194.2	0.16	32.83	4	0	0.001025	-2.99	50% aq. ethanol	full-thickness	not available	flow-through	saline	37	24	radiolabelled (14C)	*Toxicology*, 178:65-66
17	clebopride	373.9	3.21	11.47	4	2	0.0074	-2.13	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
18	clotrimazole	344.85	6.26	11.17	2	0	0.0055	-2.26	propylene glycol	full-thickness	unknown	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215:51-56
19	cortisone	360.5	1.81	12.10	5	2	0.00017	-3.77	water	full-thickness skin	back	static	saline & thimerosal	32	not available	radiolabelled (3H)	*J.Soc.Cosmet.Chem*, 34:127-135
20	cortisone	360.5	1.81	12.10	5	2	0.00122	-2.91	water	full-thickness skin	abdomen	static	saline & thimerosal	32	not available	radiolabelled (3H)	*J.Soc.Cosmet.Chem*, 34:127-135
21	cortisone	360.5	1.81	12.10	5	2	0.00047	-3.33	water	full-thickness skin	abdomen	static	saline & thimerosal	32	not available	radiolabelled (3H)	*J.Soc.Cosmet.Chem*, 34:127-135

No	Name	MW	Log P KOWWIN	SP (cal/cm^3) 1/2	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Reference
22	coumarin	146.15	1.51	11.91	1	0	0.00076	-3.12	ethanol	full-thickness skin	dorsal	flow-through	HEPES buffered HBSS & 0.5% gentamycin	32(skin)	72	radiolabelled	*Toxicol.Appl.Pharmacol*,145:34-42
23	coumarin	146.15	1.51	11.91	1	0	0.00079	-3.1	ethanol	full-thickness skin	dorsal	flow-through	HEPES buffered HBSS & 0.5% gentamycin	32(skin)	72	radiolabelled	*Toxicol.Appl.Pharmacol*,145:34-42
24	o-cresyl glycidyl ether (oCGE)	164.2	2.16	10.38	2	0	0.000134	-3.87	acetone	dermatomed skin	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32	24	radiolabelled (14C)	*Xenobiotica*,30:469-483
25	decane	142.3	5.25	7.58	0	0	9.3 E-05	-4.03	JP-8	dermatom. 0.56 mm	back	static	6% Volpo 20 in PBS	not available	4	GC	*Toxicol.Sci.*, 55:247-255
26	DDT	354.49	6.79	9.45	0	0	0.0068	-2.17	acetone	dermatomed 0.5mm	back	flow-through	Hanks HEPES buffered medium, 4% BSA & gentamycin	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8:1225-1232
27	DEHP	390.57	8.39	9.39	2	0	0.000946	-3.02	acetone	isol. epidermis	back	flow-through	50% aq. ethanol	31.5 (skin)	72	radiolabelled (14C)	*Toxicol.Vitro*, 12:47-55
28	DEHP	390.57	8.39	9.39	2	0	0.0000983	-4.01	acetone	isol.dermis	back	flow-through	50% aq. ethanol	31.5 (skin)	72	radiolabelled (14C)	*Toxicol.Vitro*, 12:47-55
29	DEHP	390.57	8.39	9.39	2	0	0.000013	-4.89	acetone	isol. epidermis	back	flow-through	PBS	31.5 (skin)	72	radiolabelled (14C)	*Toxicol.Vitro*, 12:47-55
30	DEHP	390.57	8.39	9.39	2	0	0.0000476	-4.32	acetone	isol.dermis	back	flow-through	PBS	31.5 (skin)	72	radiolabelled (14C)	*Toxicol.Vitro*, 12:47-55
31	DEP	222.24	2.65	10.51	2	0	0.00037	-3.43	none	isol. epidermis	abdomen	static	50% aq. ethanol	30 (not available)	8	radiolabelled (14C)	*Environ.Health Perspect.*, 74:223-227
32	dibutylphthalate	278.35	5.11	10.86	2	0	0.000037	-4.43	none	full-thickness skin	dorsal	static	RPMI & 2% bovine albumin & 1% antibiotics	36	24	radiolabelled (14C)	*Drug Met.Disp.*,29:843-853
33	dibutylphthalate	278.35	5.11	10.86	2	0	0.000089	-4.05	none	isol. epidermis	abdomen	static	50% aq. ethanol	30 (not available)	8	radiolabelled (14C)	*Environ.Health Perspect.*, 74:223-227
34	diethylene glycol monomethyl ether	120.2	-1.5	10.25	3	1	0.08	-1.09	JP-8	dermatomed 0.56 mm	back	static	6% VOLPO 20 in PBS	32 (skin)	4	GC	*Toxicol.*, 55:247-255
35	2,4 dimethylamine	266.13	0.84	9.52	3	2	0.00031	-3.51	commercial formulation Wilbur-Elis	dermat. 0.3 mm	back	flow-through	HBSS, HEPES buffer BSA& gentamycin sulphate	37	not available	radiolabelled (14C)	*Toxicol.Vitro*,11:251-262
36	dinoseb	240.22	3.67	11.10	2	1	0.0008625	-3.06	acetone	dermatomed 0.35	dorsal	static	MEM, 4% FBS, aspartic acid, serine & gentamycin	32	not available	radiolabelled (14C)	*Fundam.Appl.Toxicol.*,19:258-267
37	dinoseb	240.22	3.67	11.10	2	1	0.00115	-2.94	acetone	dermatomed 0.35	dorsal	static	MEM, 4% FBS, aspartic acid, serine & gentamycin	32	not available	radiolabelled (14C)	*Fundam.Appl.Toxicol.*,19:258-267
38	dodecane	170.34	6.23	7.69	0	0	0.000014	-4.85	JP-8	dermatomed 0.56 mm	back	static	6% Volpo 20 in PBS	32 (skin)	4	GC	*Toxicol.*, 55:247-255
39	dodecyl decaethoxylate	482.9	4.33	not calc.	not calc.	not calc.	0.000429	-3.37	methanol	dermatomed 0.24 mm	dorsal	static	aq. ethanol	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
40	dodecyl decaethoxylate	482.9	4.33	not calc.	not calc.	not calc.	0.0000049	-5.31	methanol	dermatomed 0.24 mm	dorsal	flow-through	MEM, penicillin & streptomycin	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
41	dodecyl decaethoxylate	482.9	4.33	not calc.	not calc.	not calc.	0.000429	-3.37	methanol	dermatomed 0.28 mm	dorsal	static	50% aq. ethanol	35	24	radiolabelled (14C)	*Arch.Toxicol.*, 69:649-654
42	dodecyl glycidyl ether (C12GE)	242.2	5.01	8.41	2	0	0.000029	-4.54	acetone	dermatomed skin	dorsal	flow-through	HEPES, HBSS & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
43	dodecyl monoethoxylate	230.4	4.5	9.16	2	1	0.00546	-2.26	methanol	dermatomed 0.24 mm	dorsal	static	aq. ethanol	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
44	dodecyl monoethoxylate	230.4	4.5	9.16	2	1	0.00000032	-6.49	methanol	dermatomed 0.24 mm	dorsal	flow-through	MEM, penicillin & streptomycin	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
45	domperidone	425.92	3.35	12.48	3	2	0.0028	-2.55	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
46	epikote YX4000	354.4	5.19	11.00	4	0	0.098	-1.01	acetone	dermatomed skin	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
47	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.00000396	-5.4	40% propylene glycol	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
48	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.00001322	-4.88	propylene glycol & dode-cylazacycloheptan-2-one	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
49	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.00000542	-5.27	40% propylene glycol & 5% dimethylsulphoxide	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472

No	Name	MW	Log P KOWWIN	SP (cal/cm^3) 1/2	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Reference
50	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.000075	-4.12	40% propylene glycol & 2.25% sodium lauryl sulphate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol*., 42:468-472
51	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.0000099	-5.00	40% propylene glycol & 1% dodecyl-L-pyroglutamate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol*., 42:468-472
52	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.00002	-4.70	40% propylene glycol & 10% N-methyl-2-pyrrolidone	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol*., 42:468-472
53	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.0000197	-4.70	40% propylene glycol & 12% N-methyl-2-pyrrolidone	full-thickness	abdomen	static	saline	37	26	spectrophotometry	*J.Pharm.Pharmacol*., 42:468-472
54	ethanol	46.07	-0.14	10.92	1	1	0.000415	-3.38	water	full-thickness	back	static	saline	30	6	radiolabelled (14C)	*J.Invest.Dermatol.*, 96:921-925
55	ethylaniline	121.2	2.11	9.73	1	1	0.115	-0.94	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100:1-7
56	ethyl benzene	106.2	3.03	9.04	0	0	0.00031	-3.51	JP-8	dermat. 0.56 mm	back	static	6% Volpo 20 in PBS	32 (skin)	4	GC	*Toxicol.* Sci, 55:247-255
57	2-ethoxyethanol	90.12	-0.42	10.33	2	1	0.000078	-4.11	methanol	dermat. 0.33 mm	dorsal	flow-through	MEM sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl. Pharmacol*., 180:74-82
58	2-ethoxyethanol	90.12	-0.42	10.33	2	1	0.00023	-3.64	methanol	full-thickness	dorsal	flow-through	MEM sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl. Pharmacol*., 180:74-82
59	2-ethoxyethanol	90.12	-0.42	10.33	2	1	0.000148	-3.83	none	dermat. 0.33 mm	dorsal	flow-through	MEM sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl. Pharmacol*., 180:74-82
60	2-ethoxyethanol	90.12	-0.42	10.33	2	1	0.000075	-4.12	none	full-thickness	dorsal	flow-through	MEM sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl. Pharmacol*., 180:74-82
61	felodipine	384.3	3.86	10.43	3	1	0.004	-2.40	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
62	fenoxapropethyl	361.78	4.95	11.06	5	0	0.00071	-3.15	acetone	dermatom. 0.6 mm	back	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 6:53-59
63	fenoxapropethyl	361.78	4.95	11.06	5	0	0.00035	-3.46	acetone	dermatom. 0.9 mm	back	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 6:53-59
64	fenoxapropethyl	361.78	4.95	11.06	5	0	0.00035	-3.46	acetone	dermatom. 0.8 mm	back	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 6:53-59
65	haloperidol	375.9	4.22	10.78	4	1	0.02	-1.70	lactic acid & antibacterial antimycotic solution	full-thickness	abdomen	flow-through	0.03% v/v lactic acid solution	37	48	RP HPLC	*Int.J.Pharm.*, 212: 247-255
66	1,6-hexanediol diglycidyl ether (HDDGE)	230.2	0.84	9.36	4	0	0.000402	-3.40	acetone	dermatomed	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (14C)	*Xenobiotica*, 30: 469-483
67	4-n-hexylaniline	177.3	4.08	9.68	1	1	0.229	-0.64	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100:1-7
68	hydroquinone	110.11	1.03	15.18	2	2	2.26 E-05	-4.66	not available	full-thickness	abdomen	static	Dulbecco's PBS, antibiotics and fungicides	30	8	radiolabelled (14C)	*Toxicol.Lett.*,80:167-172
69	ketoprofen	254.29	3.12	11.75	2	1	0.0187	-1.73	IPM	full-thickness	not available	static	ethanol	32	8	HPLC	*Int.J.Pharm.*, 262-13-22
70	linoleic acid	289.45	7.51	9.05	1	1	0.000029	-4.54	ethanol	full-thickness	sides, abdomen and back	static	phosphate buffer & pluronic F68 & BHT	37	95	radiolabelled (14C)	*J.Pharm.Pharmacol*. 34:610-611
71	lorazepam	321.16	2.41	12.91	3	2	0.000051	-4.29	50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
72	lorazepam	321.16	2.41	12.91	3	2	0.0001146	-3.94	0.5% tween 80 & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
73	lorazepam	321.16	2.41	12.91	3	2	0.000078	-4.11	5% tween 80 & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
74	lorazepam	321.16	2.41	12.91	3	2	0.0001994	-3.70	0.5% benzalkonium Cl & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
75	lorazepam	321.16	2.41	12.91	3	2	0.0003591	-3.44	5% benzalkonium Cl & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
76	lorazepam	321.16	2.41	12.91	3	2	0.0001501	-3.82	0.5% SLS & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
77	lorazepam	321.16	2.41	12.91	3	2	0.0005662	-3.25	5% SLS & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369

No	Name	MW	Log P KOWWIN	SP (cal/cm^3) 1/2	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Reference
78	mannitol	182.17	-3.01	18.53	6	6	0.000323	-3.49	dist. water	full-thickness	dorsal	static	0.9% physiological saline	30	96	radiolabelled (14C)	*Pharm.Res*, 9:884-887
79	mannitol	182.17	-3.01	18.53	6	6	0.00023	-3.64	dist. water	isol. epidermis	dorsal	static	0.9% physiological saline	30	96	radiolabelled (14C)	*Pharm.Res*, 9:884-887
80	mannitol	182.17	-3.01	18.53	6	6	0.000579	-3.24	dist. water	full-thickness	dorsal	static	0.9% physiological saline	not available	not available	radiolabelled (14C)	*Toxicol.Vitro*,8:827-830
81	mannitol	182.17	-3.01	18.53	6	6	0.00087	-3.06	dist. water	isol. epidermis	dorsal	static	0.9% physiological saline	not available	not available	radiolabelled (14C)	*Toxicol.Vitro*,8:827-830
82	mannitol	182.17	-3.01	18.53	6	6	0.000905	-3.04	dist. water	isol. epidermis	dorsal		0.9% physiological saline	32	not available	radiolabelled (14C)	*Toxicol.Vitro*,8:827-830
83	mannitol	182.17	-3.01	18.63	6	6	0.000399	-3.40	dist. water	dermat. 0.23 mm	dorsal	static	0.9% physiological saline	not available	not available	radiolabelled (14C)	*Toxicol.Vitro*,8:827-830
84	mannitol	182.17	-3.01	18.63	6	6	0.000872	-3.06	dist. water	dermat. 0.23 mm	dorsal	flow-through	0.9% physiological saline	32	not available	radiolabelled (14C)	*Toxicol.Vitro*,8:827-830
85	mannitol	182.17	-3.01	18.63	6	6	0.00134	-2.87	water	full-thickness	back	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol.*, 96:921-925
86	mefenamic acid	241.29	5.28	11.85	2	0	0.0077	-2.11	IPM	full-thickness	not available	static	ethanol	32	8	HPLC	*Int.J.Pharm.*, 262-13-22
87	4-methylaniline	107.2	1.62	10.58	1	1	0.08549	-1.07	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100:1-7
88	methyl nicotinate	137.14	0.64	11.80	2	0	0.00325	-2.49	transcutol	full-thickness skin	abdomen	static	0.9~%sodium chloride	30(skin)	not available	HPLC	*J.Pharm.Sci.*, 80:54-56
89	methyl nicotinate	137.14	0.64	11.80	2	0	0.00278	-2.56	transcutol, labrafac hydrophile & DPPG	full-thickness skin	abdomen	static	0.9~%sodium chloride	30(skin)	not available	HPLC	*J.Pharm.Sci.*, 80:54-56
90	methyl nicotinate	137.14	0.64	11.80	2	0	0.00222	-2.65	labrafac hydrophile	full-thickness skin	abdomen	static	0.9~%sodium chloride	30(skin)	not available	HPLC	*J.Pharm.Sci.*, 80:54-56
91	methyl nicotinate	137.14	0.64	11.80	2	0	0.00663	-2.18	propylene glycol dipelargonate	full-thickness skin	abdomen	static	0.9~%sodium chloride	30(skin)	not available	HPLC	*J.Pharm.Sci.*, 80:54-56
92	2-(2-methoxyethoxy) ethanol	120.15	-1.18	10.25	3	1	0.08	-1.10	JP-8	dermat. 0.56 mm	back	static	6% Volpo 20 in PBS	32 (skin)	4	GC	*Toxicol.Sci.*,55:247-255
93	metochloropramide	354.3	1.69	11.13	4	2	0.0091	-2.04	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
94	metopimazine	445.61	2.42	13.55	3	1	0.0051	-2.29	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
95	N-N-diethyl m-toluamide	191.28	2.26	10.70	1	0	0.00168	-2.77	acetone	dermat.0.5mm	back	flow-through	sterile Ringer's solution, Trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol.Vitro*,7:141-148
96	naphthalene	128.2	3.17	10.42	0	0	0.00051	-3.29	JP-8	dermat.0.56mm	back	static	6% Volpo 20 in PBS	32(skin)	4	GC	*Toxicol.Sci.*55:247-255
97	nicardipine	479.54	3.9	10.87	5	1	0.0049	-2.31	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
98	nicorandil	211.18	0.43	14.40	3	1	0.000727	-3.14	water	full-thickness	abdomen	static	saline	37	32	HPLC	*J.Pharm.Pharmacol.*, 41:379-383
99	nifedipine	346.3	4.04	10.92	4	0	0.0017	-2.77	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
100	nimodipine	418.4	3.13	10.50	3	1	0.0026	-2.59	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
101	nitrendipine	360.4	2.99	11.44	5	1	0.0039	-2.41	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
102	nonane	128.3	4.76	7.51	0	0	0.000042	-4.38	JP-8	dermatom. 0.56 mm	back	static	6% Volpo in PBS	32 (skin)	4	GC	*Toxicol.Sci.*55:247-255
103	paraquat	257.16	-2.71	10.45	0	0	0.000346	-3.46	water	full-thickness	back	static	saline	30	6	radiolabelled (14C)	*J.Invest.Dermatol.*.96:921-925
104	4-n-pentylaniline	163.3	3.59	9.79	1	1	0.248	-0.61	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100:1-7
105	2-phenoxyethanol	138.17	1.1	11.49	2	1	0.00272	-2.57	methanol	dermatom.0.24 mm	dorsal	static	50& aq. ethanol	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016

No	Name	MW	Log P KOWWIN	SP (cal/cm^3) 1/2	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Reference
106	2-phenoxyethanol	138.17	1.1	11.49	2	1	2.72E -05	-4.57	methanol	dermatom.0.24 mm	dorsal	static	aq. ethanol	37	24	radiolabelled (14C)	*Toxicol.Vitro,* 12:57-65
107	2-phenoxyethanol	138.17	1.1	11.49	2	1	1.76E-05	-4.75	methanol	dermatom.0.24 mm	dorsal	flow-through	MEM & penicillin / streptomycin + CO2	37	24	radiolabelled (14C)	*Toxicol.Vitro,* 12:57-65
108	2-phenoxyethanol	138.17	1.1	11.49	2	1	0.001764	-2.75	methanol	dermatom.0.24 mm	dorsal	flow-through	MEM & penicillin / streptomycin + CO2	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016
109	2-phenoxyethanol	138.17	1.1	11.49	2	1	0.00735	-2.13	methanol	dermatom.0.24 mm	dorsal	static	50& aq. ethanol	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016
110	2-phenylphenol	170.21	3.28	12.24	1	1	0.00097	-3.01	60% aq. ethanol	full-thickness skin	dorsal / flank	static	MEM, 10% heat- inactivated BSA, 2mM l-glutamine & 0.05mg/ml gentamycine	32	48	radiolabelled (14C)	*Toxicol.Pharmacol.*35:198-208
111	2-phenylphenol	170.21	3.28	12.24	1	1	0.0266	-1.58	60% aq. ethanol	isolated epidermis	dorsal / flank	static	saline (0.9%NaCl), 0.01% sodium azide & 3%BSA	32	48	radiolabelled (14C)	*Toxicol.Pharmacol.*35:198-208
112	4-n-propylaniline	135	2.61	10.10	1	1	0.169	-0.77	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100:1-7
113	propoxur	209.25	1.9	10.31	2	1	0.00052	-3.28	60% aq. ethanol	full-thickness	dorsal	static	culture medium 10% fetal Bovine serum	32	24	radiolabelled (14C)	*Toxicol.Sci.* 58:15-22
114	propoxur	209.25	1.9	10.31	2	1	0.00375	-2.43	60% aq. ethanol	isol. epidermis	dorsal	static	saline & sodium azide, BSA	32	24	radiolabelled (14C)	*Toxicol.Sci.* 58:15-22
115	salicylamide	137.14	1.03	16.60	2	2	0.000017	-4.77	dimethyl isosoride & 2-propanol	full-thickness	not available	static	isotonic phosphate buffer	32 (skin)	48	HPLC	*Eur.J.Pharm.Sci.*., 17:95-104
116	salicylic acid	138.1	2.24	14.39	2	2	0.01046	-1.98	phosphate buffer (pH2)	full-thickness	dorsal	static	tris.HCL buffer sol.	25.	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418
117	salicylic acid	138.1	2.24	14.39	2	2	0.0073	-2.14	citric acid phosphate (pH3)	full-thickness	dorsal	static	tris.HCL buffer sol.	25.	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418
118	salicylic acid	138.1	2.24	14.39	2	2	0.00132	-2.88	citric acid phosphate (pH4)	full-thickness	dorsal	static	tris.HCL buffer sol.	25.	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418
119	salicylic acid	138.1	2.24	14.39	2	2	0.0248	-1.61	citric acid phosphate (pH2)	full-thickness	dorsal	static	tris.HCL buffer sol.	25.	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, 45: 414-418
120	salicylic acid	138.1	2.24	14.39	2	2	0.000024	-4.62	dimethyl isosoride & 2-propanol	full-thickness	not available	static	isotonic phosphate buffer	32 (skin)	48	HPLC	*Eur.J.Pharm.Sci.*., 17:95-104
121	scopolamine	303.4	0.39	11.53	4	1	0.0041	-2.39	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
122	terbinafine	291.4	5.81	9.33	1	0	0.055	-1.26	propylene glycol	full-thickness	unknown	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215:51-56
123	testosterone	288.4	3.27	10.66	2	1	0.0002	-3.70	ethanol	isol. epidermis	abdomen	static	culture medium &10% BSA	32	22	radiolabelled (14C)	Van de Sandt 2000
124	testosterone	288.4	3.27	10.66	2	1	0.0018	-2.74	20% aq. ethanol	full-thickness	dorsal	static	saline & 40% polyethylene glycol	37 (not available)	24	HPLC & UV detector	*J.Pharm.Pharmacol.*, 52: 369-375
125	testosterone	288.4	3.27	10.66	2	1	0.00013	-3.89	40% aq. ethanol	full-thickness	dorsal	static	saline & 40% polyethylene glycol	37 (not available)	24	HPLC & UV detector	*J.Pharm.Pharmacol.*, 52: 369-375
126	testosterone	288.4	3.27	10.66	2	1	0.00007	-4.15	50% aq. ethanol	full-thickness	dorsal	static	saline & 40% polyethylene glycol	37 (not available)	24	HPLC & UV detector	*J.Pharm.Pharmacol.*, 52: 369-375
127	testosterone	288.4	3.27	10.66	2	1	0.00002	-4.70	80% aq. ethanol	full-thickness	dorsal	static	saline & 40% polyethylene glycol	37 (not available)	24	HPLC & UV detector	*J.Pharm.Pharmacol.*, 52: 369-375
128	theophylline	180.17	-0.39	14.05	4	1	0.00923	-2.03	1-propanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242
129	theophylline	180.17	-0.39	14.05	4	1	0.0109	-1.96	ethanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242
130	theophylline	180.17	-0.39	14.05	4	1	0.0139	-1.86	methanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242
131	theophylline	180.17	-0.39	14.05	4	1	0.0022	-2.66	water	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242
132	toluene (methyl benzene)	92.1	2.54	9.14	0	0	0.0011	-2.96	JP-8	dermatom. 0.56 mm	back	static	6% Volpo 20 in PBS	32(skin)	4	GC	*Toxicol.* Sci., 55:247-255
133	triclosan	289.55	2.47	10.02	2	1	1.3609	0.13	90% aq. ethanol	dermatomed 0.28 mm	dorsal	flow-through	Eagles MEM & Earles salts buffered to pH7.3	32	24	radiolabelled (14C)	*J.Pharmacol.Exp.Ther.*, 38:361-370

No	Name	MW	Log P KOWWIN	SP (cal/cm^3) 1/2	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Reference
134	tridecane	185.4	6.73	7.74	0	0	0.000015	-4.82	JP-8	dermatomed 0.56 mm	back	static	6% Volpo 20 in PBS	32(skin)	4	GC	*Toxicol.* Sci., 55:247-255
135	undecane	156.31	5.74	7.64	0	0	0.000025	-4.60	JP-8	dermatom. 0.56 mm	back	static	6% Volpo 20 in PBS	32(skin)	4	GC	*Toxicol.* Sci., 55:247-255
136	xylene (dimethyl benzene)	106.2	3.09	9.10	0	0	0.00017	-3.77	JP-8	dermatom. 0.56 mm	back	static	6% Volpo 20 in PBS	32(skin)	4	GC	*Toxicol.* Sci., 55:247-255
137	water	18.02	-1.38	26.68	1	1	0.00738	-2.13	0.9% saline	isol. epidermis	back	flow-through	50% aq. ethanol	31.5 (skin)	5	radiolabelled (3H)	*Toxicol.Vitro*, 12:47-55
138	water	18.02	-1.38	26.68	1	1	0.00175	-2.77	0.9% saline	isol. epidermis	back	flow-through	PBS	31.5 (skin)	5	radiolabelled (3H)	*Toxicol.Vitro*, 12:47-55
139	water	18.02	-1.38	26.68	1	1	0.0517	-1.29	0.9% saline	isol.dermis	back	flow-through	PBS	31.5 (skin)	5	radiolabelled (3H)	*Toxicol.Vitro*, 12:47-55
140	water	18.02	-1.38	26.68	1	1	0.00143	-2.84	0.9% physiological saline	full-thickness	dorsal	static	0.9 % physiological saline	30	96	radiolabelled (14C)	*Pharmaceut.Res.*,9:884-887
141	water	18.02	-1.38	26.68	1	1	0.00116	-2.94	0.9% physiological saline	isol. epidermis	dorsal	static	0.9 % physiological saline	30	96	radiolabelled (14C)	*Pharmaceut.Res.*,9:884-887
142	water	18.02	-1.38	26.68	1	1	0.00194	-2.71	saline	full-thickness	dorsal	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8: 827-830
143	water	18.02	-1.38	26.68	1	1	0.0014	-2.85	saline	isol. epidermis	dorsal	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8: 827-830
144	water	18.02	-1.38	26.68	1	1	0.00198	-2.7	dist. water	dermatomed 0.23 mm	dorsal	flow-through	0.9% physiological saline	32	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8: 827-830
145	urea	60.6	-1.56	14.36	1	2	0.000016	-4.80	petrolatum	full-thickness	back	static	saline & thimerosol	32	not available	radiolabelled (14C)	*Toxicol.Appl.Pharmacol*,62:474-480
146	urea	60.6	-1.56	14.36	1	2	0.00016	-3.80	water	full-thickness	back	static	saline & thimerosol	32	not available	radiolabelled (14C)	*J.Soc.Cosmet.Chem.*,34: 127-135
147	urea	60.6	-1.56	14.36	1	2	0.00188	-2.73	water	full-thickness	abdomen	static	saline & thimerosol	32	not available	radiolabelled (14C)	*J.Soc.Cosmet.Chem.*,34: 127-135

Group B6

Type of skin: rat Site: all sites 30°C-32° C Time HPLC / GC / radiolabelled Vehicle: any Receptor fluid any

Cell type: static / flow-through

No	Name	MW	Log P KOWWIN	SP (cal/cm^3)$^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	ethanol	46.07	-0.14	10.92	1	1	0.000415	-3.38	water	full-thickness	back	static	saline	30	6	radiolabelled (14C)	*J.Invest.Dermatol.*, 96:921-925
2	hydroquinone	110.11	1.03	15.18	2	2	2.26 E-05	-4.66	not available	full-thickness	abdomen	static	Dulbecco's PBS, antibiotics and fungicides	30	8	radiolabelled (14C)	*Toxicol.Lett.*,80:167-172
3	mannitol	182.17	-3.01	18.53	6	6	0.000323	-3.49	dist. water	full-thickness	dorsal	static	0.9% physiological saline	30	96	radiolabelled (14C)	*Pharm.Res*, 9:884-887
4	mannitol	182.17	-3.01	18.53	6	6	0.00023	-3.64	dist. water	isol. epidermis	dorsal	static	0.9% physiological saline	30	96	radiolabelled (14C)	*Pharm.Res*, 9:884-887
5	mannitol	182.17	-3.01	18.63	6	6	0.00134	-2.87	water	full-thickness	back	static	saline	30	6	radiolabelled (14C)	*J.Investig.Dermatol.*, 96:921-925
6	paraquat	257.16	-2.71	10.45	0	0	0.000346	-3.46	water	full-thickness	back	static	saline	30	6	radiolabelled (14C)	*J.Invest.Dermatol.*::96:921-925
7	water	18.02	-1.38	26.68	1	1	0.00143	-2.84	0.9% physiological saline	full-thickness	dorsal	static	0.9 % physiological saline	30	96	radiolabelled (14C)	*Pharmaceut.Res.*,9:884-887
8	water	18.02	-1.38	26.68	1	1	0.00116	-2.94	0.9% physiological saline	isol. epidermis	dorsal	static	0.9 % physiological saline	30	96	radiolabelled (14C)	*Pharmaceut.Res.*,9:884-887
9	aminopyrene	231	0.6	10.7	3	0	0.033	-1.48	IPM	full-thickness	not available	static	ethanol	32	8	HPLC	*Int.J.Pharm.*, 262-13-22
10	benzoic acid	122.1	1.87	11.94	1	1	0.00035	-3.46	petrolatum	full-thickness	back	static	saline & thimerosol	32	not available	radiolabelled (14C)	*Toxicol.Appl.Pharmacol.*,62:474-480

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
11	benzoic acid	122.1	1.87	11.94	1	1	0.00029	-3.54	petrolatum	full-thickness	abdomen	static	saline & thimerosol	32	not available	radiolabelled (14C)	*J.Soc.Cosmet.Chem.*,34:127-135
12	bufexamac	223.3	1.98	12.43	3	2	0.271	-0.57	IPM	full-thickness	not available	static	ethanol	32	8	HPLC	*Int.J.Pharm.*, 262-13-22
13	caffeine	194.2	0.16	32.83	4	0	0.00031	-3.51	petrolatum	full-thickness	back	static	saline & thimerosol	32	not available	radiolabelled (14C)	*Toxicol.Appl.Pharmacol*,62: 474-480
14	clotrimazole	344.85	6.26	11.17	2	0	0.0055	-2.26	propylene glycol	full-thickness	unknown	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215:51-56
15	cortisone	360.5	1.81	12.10	5	2	0.00017	-3.77	water	full-thickness skin	back	static	saline & thimerosal	32	not available	radiolabelled (3H)	*J.Soc.Cosmet.Chem*, 34:127-135
16	cortisone	360.5	1.81	12.10	5	2	0.00122	-2.91	water	full-thickness skin	abdomen	static	saline & thimerosal	32	not available	radiolabelled (3H)	*J.Soc.Cosmet.Chem*, 34:127-135
17	cortisone	360.5	1.81	12.10	5	2	0.00047	-3.33	water	full-thickness skin	abdomen	static	saline & thimerosal	32	not available	radiolabelled (3H)	*J.Soc.Cosmet.Chem*, 34:127-135
18	o-cresyl glycidyl ether (oCGE)	164.2	2.16	10.38	2	0	0.000134	-3.87	acetone	dermatomed skin	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32	24	radiolabelled (14C)	*Xenobiotica*,30:469-483
19	dinoseb	240.22	3.67	11.10	2	1	0.0008625	-3.06	acetone	dermatomed 0.35	dorsal	static	MEM, 4% FBS, aspartic acid, serine & gentamycin	32	not available	radiolabelled (14C)	*Fundam.Appl.Toxicol.*,19:258-267
20	dinoseb	240.22	3.67	11.10	2	1	0.00115	-2.94	acetone	dermatomed 0.35	dorsal	static	MEM, 4% FBS, aspartic acid, serine & gentamycin	32	not available	radiolabelled (14C)	*Fundam.Appl.Toxicol.*,19:258-267
21	epikote YX4000	354.4	5.19	11.00	4	0	0.098	-1.01	acetone	dermatomed skin	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32	24	radiolabelled (14C)	*Xenobiotica*, 30:469-483
22	2-ethoxyethanol	90.12	-0.42	10.33	2	1	0.000078	-4.11	methanol	dermat. 0.33 mm	dorsal	flow-through	MEM sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl. Pharmacol.*, 180:74-82
23	2-ethoxyethanol	90.12	-0.42	10.33	2	1	0.00023	-3.64	methanol	full-thickness	dorsal	flow-through	MEM sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl. Pharmacol.*, 180:74-82
24	2-ethoxyethanol	90.12	-0.42	10.33	2	1	0.000148	-3.83	none	dermat. 0.33 mm	dorsal	flow-through	MEM sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl. Pharmacol.*, 180:74-82
25	2-ethoxyethanol	90.12	-0.42	10.33	2	1	0.000075	-4.12	none	full-thickness	dorsal	flow-through	MEM sodium bicarbonate & gentamycin sulphate	32	24	radiolabelled (14C)	*Toxicol. Appl. Pharmacol.*, 180:74-82
26	ketoprofen	254.29	3.12	11.75	2	1	0.0187	-1.73	IPM	full-thickness	not available	static	ethanol	32	8	HPLC	*Int.J.Pharm.*, 262-13-22
27	mannitol	182.17	-3.01	18.53	6	6	0.000905	-3.04	dist. water	isol. epidermis	dorsal	not available	0.9% physiological saline	32	not available	radiolabelled (14C)	*Toxicol.Vitro*,8:827-830
28	mannitol	182.17	-3.01	18.63	6	6	0.000872	-3.06	dist. water	dermat. 0.23 mm	dorsal	flow-through	0.9% physiological saline	32	not available	radiolabelled (14C)	*Toxicol.Vitro*,8:827-830
29	mefenamic acid	241.29	5.28	11.85	2	0	0.0077	-2.11	IPM	full-thickness	not available	static	ethanol	32	8	HPLC	*Int.J.Pharm.*, 262-13-22
30	2-phenylphenol	170.21	3.28	12.24	1	1	0.00097	-3.01	60% aq. ethanol	full-thickness skin	dorsal / flank	static	MEM, 10% heat- inactivated BSA, 2mM l-glutamine & 0.05mg/ml gentamycine	32	48	radiolabelled (14C)	*Toxicol.Pharmacol.*35:198-208
31	2-phenylphenol	170.21	3.28	12.24	1	1	0.0266	-1.58	60% aq. ethanol	isolated epidermis	dorsal / flank	static	saline (0.9%NaCl), 0,01% sodium azide & 3% BSA	32	48	radiolabelled (14C)	*Toxicol.Pharmacol.*35:198-208
32	propoxur	209.25	1.9	10.31	2	1	0.00052	-3.28	60% aq. ethanol	full-thickness	dorsal	static	culture medium 10% fetal Bovine serum	32	24	radiolabelled (14C)	*Toxicol.Sci.* 58:15-22
33	propoxur	209.25	1.9	10.31	2	1	0.00375	-2.43	60% aq. ethanol	isol. epidermis	dorsal	static	saline & sodium azide, BSA	32	24	radiolabelled (14C)	*Toxicol.Sci.* 58:15-22
34	terbinafine	291.4	5.81	9.33	1	0	0.055	-1.26	propylene glycol	full-thickness	unknown	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215:51-56
35	testosterone	288.4	3.27	10.66	2	1	0.0002	-3.70	ethanol	isol. epidermis	abdomen	static	culture medium &10% BSA	32	22	radiolabelled (14C)	Van de Sandt 2000
36	triclosan	289.55	2.47	10.02	2	1	1.3609	0.13	90% aq. ethanol	dermatomed 0.28 mm	dorsal	flow-through	Eagles MEM & Earles salts buffered to pH7.3	32	24	radiolabelled (14C)	*J.Pharmacol.Exp.Ther.*, 38:361-370
37	water	18.02	-1.38	26.68	1	1	0.00198	-2.7	dist. water	dermatomed 0.23 mm	dorsal	flow-through	0.9% physiological saline	32	not available	radiolabelled (3H)	*Toxicol.Vitro*, 8: 827-830
38	urea	60.6	-1.56	14.36	1	2	0.000016	-4.80	petrolatum	full-thickness	back	static	saline & thimerosol	32	not available	radiolabelled (14C)	*Toxicol.Appl.Pharmacol*,62:474-480

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
39	urea	60.6	-1.56	14.36	1	2	0.00016	-3.80	water	full-thickness	back	static	saline & thimerosol	32	not available	radiolabelled (14C)	*J.Soc.Cosmet.Chem.*,34: 127-135
40	urea	60.6	-1.56	14.36	1	2	0.00188	-2.73	water	full-thickness	abdomen	static	saline & thimerosol	32	not available	radiolabelled (14C)	*J.Soc.Cosmet.Chem.*,34: 127-135

Group B7

Type of skin: rat Site: all sites 37° C Time HPLC / GC / radiolabelled Vehicle: any Receptor fluid any

Cell type: static / flow-through

No	Name	MW	Log P KOWWIN	SP (cal/cm^3) 1/2	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	alizapride	339.9	1.8	12.06	6	2	0.0057	-2.24	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
2	aniline	93	1.08	10.83	1	1	0.067	-1.17	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100:1-7
3	bromopride	344.26	1.94	10.74	4	2	0.0078	-2.11	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
4	4-n-butylaniline	149	3.1	9.51	1	1	0.23	-0.64	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100:1-7
5	caffeine	194.2	0.16	32.83	4	0	0.001025	-2.99	50% aq. ethanol	full-thickness	not available	flow-through	saline	37	24	radiolabelled (14C)	*Toxicology*, 178:65-66
6	clebopride	373.9	3.21	11.47	4	2	0.0074	-2.13	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
7	DDT	354.49	6.79	9.45	0	0	0.0068	-2.17	acetone	dermatomed 0.5mm	back	flow-through	Hanks HEPES buffered medium, 4% BSA & gentamycin	37	48	radiolabelled (14C)	*Toxicol.Vitro*, 8:1225-1232
8	2,4 dimethylamine	266.13	0.84	9.52	3	2	0.00031	-3.51	commercial formulation Wilbur-Elis	dermat. 0.3 mm	back	flow-through	HBSS, HEPES buffer BSA& gentamycin sulphate	37	not available	radiolabelled (14C)	*Toxicol.Vitro*,11:251-262
9	dodecyl decaethoxylate	482.9	4.33	not calc.	not calc.	not calc.	0.000429	-3.37	methanol	dermatomed 0.24 mm	dorsal	static	aq. ethanol	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
10	dodecyl decaethoxylate	482.9	4.33	not calc.	not calc.	not calc.	0.0000049	-5.31	methanol	dermatomed 0.24 mm	dorsal	flow-through	MEM, penicillin & streptomycin	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
11	dodecyl monoethoxylate	230.4	4.5	9.16	2	1	0.00546	-2.26	methanol	dermatomed 0.24 mm	dorsal	static	aq. ethanol	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
12	dodecyl monoethoxylate	230.4	4.5	9.16	2	1	0.00000032	-6.49	methanol	dermatomed 0.24 mm	dorsal	flow-through	MEM, penicillin & streptomycin	37	24	radiolabelled (14C)	*Toxicol.Vitro*, 12:57-65
13	domperidone	425.92	3.35	12.48	3	2	0.0028	-2.55	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
14	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.00000396	-5.4	40% propylene glycol	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
15	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.00001322	-4.88	propylene glycol & dodecylazacycloheptan-2-one	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
16	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.00000542	-5.27	40% propylene glycol & 5% dimethylsulphoxide	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
17	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.000075	-4.12	40% propylene glycol & 2.25% sodium lauryl sulphate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
18	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.0000099	-5.00	40% propylene glycol & 1% dodecyl-L-pyroglutamate	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
19	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.00002	-4.70	40% propylene glycol & 10% N-methyl-2-pyrrolidone	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
20	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.0000197	-4.70	40% propylene glycol & 12% N-methyl-2-pyrrolidone	full-thickness	abdomen	static	saline	37	26	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
21	ethylaniline	121.2	2.11	9.73	1	1	0.115	-0.94	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100:1-7

No	Name	MW	Log P KOWWIN	SP (cal/cm^3) 1/2	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
22	felodipine	384.3	3.86	10.43	3	1	0.004	-2.40	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
23	fenoxapropethyl	361.78	4.95	11.06	5	0	0.00071	-3.15	acetone	dermatom. 0.6 mm	back	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol. Vitro*, 6:53-59
24	fenoxapropethyl	361.78	4.95	11.06	5	0	0.00035	-3.46	acetone	dermatom. 0.9 mm	back	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol. Vitro*, 6:53-59
25	fenoxapropethyl	361.78	4.95	11.06	5	0	0.00035	-3.46	acetone	dermatom. 0.8 mm	back	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol. Vitro*, 6:53-59
26	haloperidol	375.9	4.22	10.78	4	1	0.02	-1.70	lactic acid & antibacterial antimycotic solution	full-thickness	abdomen	flow-through	0.03% v/v lactic acid solution	37	48	RP HPLC	*Int.J.Pharm.*, 212: 247-255
27	4-n-hexylaniline	177.3	4.08	9.68	1	1	0.229	-0.64	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100:1-7
28	linoleic acid	289.45	7.51	9.05	1	1	0.000029	-4.54	ethanol	full-thickness	sides, abdomen and back	static	phosphate buffer & pluronic F68 & BHT	37	95	radiolabelled (14C)	*J.Pharm.Pharmacol.* 34:610-611
29	lorazepam	321.16	2.41	12.91	3	2	0.000051	-4.29	50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
30	lorazepam	321.16	2.41	12.91	3	2	0.0001146	-3.94	0.5% tween 80 & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
31	lorazepam	321.16	2.41	12.91	3	2	0.000078	-4.11	5% tween 80 & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
32	lorazepam	321.16	2.41	12.91	3	2	0.0001994	-3.70	0.5% benzalkonium Cl & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
33	lorazepam	321.16	2.41	12.91	3	2	0.0003591	-3.44	5% benzalkonium Cl & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
34	lorazepam	321.16	2.41	12.91	3	2	0.0001501	-3.82	0.5% SLS & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
35	lorazepam	321.16	2.41	12.91	3	2	0.0005662	-3.25	5% SLS & 50% aq. propylene glycol	full-thickness	abdomen	static	phosphate buffer	37	24	HPLC	*Int.J.Pharm.*, 250:359-369
36	4-methylaniline	107.2	1.62	10.58	1	1	0.08549	-1.07	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100:1-7
37	metochloropramide	354.3	1.69	11.13	4	2	0.0091	-2.04	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
38	metopimazine	445.61	2.42	13.55	3	1	0.0051	-2.29	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
39	N-N-diethyl m-toluamide	191.28	2.26	10.70	1	0	0.00168	-2.77	acetone	dermat.0.5mm	back	flow-through	sterile Ringer's solution, Trizma, glucose & antibiotics	37	48	radiolabelled (14C)	*Toxicol. Vitro*,7:141-148
40	nicardipine	479.54	3.9	10.87	5	1	0.0049	-2.31	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
41	nicorandil	211.18	0.43	14.40	3	1	0.000727	-3.14	water	full-thickness	abdomen	static	saline	37	32	HPLC	*J.Pharm.Pharmacol.*, 41:379-383
42	nifedipine	346.3	4.04	10.92	4	0	0.0017	-2.77	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
43	nimodipine	418.4	3.13	10.50	3	1	0.0026	-2.59	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
44	nitrendipine	360.4	2.99	11.44	5	1	0.0039	-2.41	50% ethanol	full-thickness	dorsal	flow-through	50% ethanol	37	24	HPLC	*J.Pharm.Sci.*, 80:931-934
45	4-n-pentylaniline	163.3	3.59	9.79	1	1	0.248	-0.61	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100:1-7
46	2-phenoxyethanol	138.17	1.1	11.49	2	1	0.00272	-2.57	methanol	dermatom.0.24 mm	dorsal	static	50& aq. ethanol	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016
47	2-phenoxyethanol	138.17	1.1	11.49	2	1	2.72E -05	-4.57	methanol	dermatom.0.24 mm	dorsal	static	aq. ethanol	37	24	radiolabelled (14C)	*Toxicol. Vitro*, 12:57-65
48	2-phenoxyethanol	138.17	1.1	11.49	2	1	1.76E-05	-4.75	methanol	dermatom.0.24 mm	dorsal	flow-through	MEM & penicillin / streptomycin + CO2	37	24	radiolabelled (14C)	*Toxicol. Vitro*, 12:57-65
49	2-phenoxyethanol	138.17	1.1	11.49	2	1	0.001764	-2.75	methanol	dermatom.0.24 mm	dorsal	flow-through	MEM & penicillin / streptomycin + CO2	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016

No	Name	MW	Log P KOWWIN	SP (cal/cm^3) 1/2	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
50	2-phenoxyethanol	138.17	1.1	11.49	2	1	0.00735	-2.13	methanol	dermatom.0.24 mm	dorsal	static	50& aq. ethanol	37	24	radiolabelled (14C)	*Food Chem.Toxicol.*,35:1009-1016
51	4-n-propylaniline	135	2.61	10.10	1	1	0.169	-0.77	physiological buffered solution	isol. epidermis	not available	flow-through	saline solution buffered pH 7.4	37	not available	HPLC	*Int.J.Pharm.*, 100:1-7
52	scopolamine	303.4	0.39	11.53	4	1	0.0041	-2.39	ethanol : water (70:30) mixture	full-thickness	dorsal	flow-through	ethanol : water (70:30) mixture	37	24	HPLC	*J.Pharm.Sci.*, 83:29-32
53	theophylline	180.17	-0.39	14.05	4	1	0.00923	-2.03	1-propanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242
54	theophylline	180.17	-0.39	14.05	4	1	0.0109	-1.96	ethanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242
55	theophylline	180.17	-0.39	14.05	4	1	0.0139	-1.86	methanol	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242
56	theophylline	180.17	-0.39	14.05	4	1	0.0022	-2.66	water	dermatom. 0.45 mm	dorsal	flow-through	normal saline & 0.25% chlorobutanol	37	24	RP HPLC with UV detection	*J.Soc.Cosmet.Chem.*,40: 231-242

Appendix 7. Mouse skin dataset

Group C1

Type of skin: mouse | Site: abdomen / dorsal | 32 ºC at the surface of the skin | Time of 24-48h | HPLC / GC / radiolabelled | Vehicle: any | Receptor fluid: any

Cell type: flow through cells | 37 ºC in WB

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	atenolol	266.3	-0.03	12.49	4	3	0.048	-1.32	full-thickness	abdomen	flow-through	0.1 % sodium azide solution in dist. water	37	24	UV / spectroscopy	*Ind.J.Exp.Biol.*, 31:691-693
2	atenolol	266.3	-0.03	12.49	4	3	0.0301	-1.52	full-thickness	abdomen	flow-through	0.1 % sodium azide solution in dist. water	37	24	UV / spectroscopy	*Ind.J.Exp.Biol.*, 31:691-693
3	atenolol	266.3	-0.03	12.49	4	3	0.0351	-1.45	full-thickness	abdomen	flow-through	0.1 % sodium azide solution in dist. water	37	24	UV / spectroscopy	*Ind.J.Exp.Biol.*, 31:691-693
4	atenolol	266.3	-0.03	12.49	4	3	0.025	-1.60	full-thickness	dorsal	flow-through	0.1 % sodium azide solution in dist. water	37	24	UV / spectroscopy	*Ind.J.Exp.Biol.*, 31:691-693
5	atenolol	266.3	-0.03	12.49	4	3	0.0213	-1.67	full-thickness	dorsal	flow-through	0.1 % sodium azide solution in dist. water	37	24	UV / spectroscopy	*Ind.J.Exp.Biol.*, 31:691-693
6	o-cresyl glycidyl ether (oCGE)	164.20	2.16	10.38	2	0	0.000176	-3.75	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (^{14}C)	*Xenobiotica*, 30:469-483
7	dodecyl glycidyl ether (C12GE)	242.2	5.01	8.41	2	0	4.61E-05	-4.34	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (^{14}C)	*Xenobiotica*, 30:469-483
8	epikote YX4000	354.4	5.19	11.00	4	0	2.63 E -06	-5.58	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (^{14}C)	*Xenobiotica*, 30:469-483
9	1,6-hexanediol diglycidyl ether (HDDGE)	230.2	0.84	9.36	4	0	5.77 E -04	-3.24	full-thickness	dorsal	flow-through	HBSS HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (^{14}C)	*Xenobiotica*, 30:469-483

Group C2

Type of skin: mouse | Site: abdomen | Temperature: any | Time any | HPLC / GC / radiolabelled | Vehicle: any | Receptor fluid: any

Cell type: flow through / static cells

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	atenolol	266.3	-0.03	12.49	4	3	0.048	-1.32	full-thickness	abdomen	flow-through	0.1 % sodium azide solution in dist. water	37	24	UV / spectroscopy	*Ind.J.Exp.Biol.*, 31:691-693
2	atenolol	266.3	-0.03	12.49	4	3	0.0301	-1.52	full-thickness	abdomen	flow-through	0.1 % sodium azide solution in dist. water	37	24	UV / spectroscopy	*Ind.J.Exp.Biol.*, 31:691-693
3	atenolol	266.3	-0.03	12.49	4	3	0.0351	-1.45	full-thickness	abdomen	flow-through	0.1 % sodium azide solution in dist. water	37	24	UV / spectroscopy	*Ind.J.Exp.Biol.*, 31:691-693
4	n-butanol	74.14	0.84	10.13	1	1	0.0065	-2.19	full-thickness	abdomen / dorsal	static	saline	not available	0.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*, 75:346-352
5	n-butanol	74.14	0.84	10.13	1	1	0.0082	-2.09	full-thickness	abdomen / dorsal	static	saline	not available	4.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,75:346-352
6	n-butanol	74.14	0.84	10.13	1	1	0.0118	-1.93	full-thickness	abdomen / dorsal	static	saline	not available	7.8	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,75:346-352
7	n-butanol	74.14	0.84	10.13	1	1	0.0124	-1.91	full-thickness	abdomen / dorsal	static	saline	not available	11.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,75:346-352
8	n-butanol	74.14	0.84	10.13	1	1	0.0119	-1.92	full-thickness	abdomen / dorsal	static	saline	not available	14.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,75:346-352
9	n-butanol	74.14	0.84	10.13	1	1	0.0115	-1.94	full-thickness	abdomen / dorsal	static	saline	not available	26.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,75:346-352

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
10	n-butanol	74.14	0.84	10.13	1	1	0.0127	-1.90	full-thickness	abdomen	static	saline	not available	2	radiolabelled (^{14}C)	*J.Soc.Cosmet.*, 35:237-252
11	caffeine	194.2	0.16	32.83	4	0	0.00026	-3.59	full-thickness	dorsal / abdominal	static	isotonic phosphate buffer & sodium azide	37	9	HPLC	*J.Cont.Release*, 33:71-77
12	corticosterone	346.5	1.99	11.91	4	2	0.00053	-3.28	full-thickness	abdomen	static	40% aq. PEG 400	37	not available	HPLC	*J.Pharm.Sci.*, 76:123-126
13	deoxycortisone	330.47	3.12	11.03	3	1	0.0034	-2.47	full-thickness	abdomen	static	40% aq. PEG 400	37	not available	HPLC	*J.Pharm.Sci.*, 76:123-126
14	ethanol	46.07	-0.14	10.92	1	1	0.0021	-2.68	full-thickness	abdomen / dorsal	static	saline	not available	0.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
15	ethanol	46.07	-0.14	10.92	1	1	0.0022	-2.66	full-thickness	abdomen / dorsal	static	saline	not available	5.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
16	ethanol	46.07	-0.14	10.92	1	1	0.0023	-2.64	full-thickness	abdomen / dorsal	static	saline	not available	10.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
17	ethanol	46.07	-0.14	10.92	1	1	0.0022	2.66	full-thickness	abdomen / dorsal	static	saline	not available	15.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
18	ethanol	46.07	-0.14	10.92	1	1	0.0021	-2.68	full-thickness	abdomen / dorsal	static	saline	not available	20.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
19	ethanol	46.07	-0.14	10.92	1	1	0.002	-2.70	full-thickness	abdomen / dorsal	static	saline	not available	25.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
20	ethanol	46.07	-0.14	10.92	1	1	0.0019	-2.72	full-thickness	abdomen / dorsal	static	saline	not available	29.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
21	ethanol	46.07	-0.14	10.92	1	1	0.0009	-3.05	full-thickness	abdomen	static	saline	not available	2	radiolabelled (^{14}C)	*J.Soc.Cosmet.*, 35:237-252
22	erioglaucine	793.86	-1.5	not calc.	not calc.	not calc.	0.00003	-4.52	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42:468-472
23	etorphine	411.55	3.02	11.76	5	2	0.0046	-2.34	full-thickness	abdominal / dorsal	static	isotonic tris buffer	37	24	radiolabelled (3H)	*Pharmaceut.Res.*, 9:963-965
24	5-fluorouracil	130.01	-0.81	13.46	3	2	0.0000603	-4.22	dermatomed 0.42 mm	abdomen	flow-through	0.002% aq. sodium azide solution	31	24	radiolabelled (3H)	*J.Investig.Pharmacol.*, 94:235-240
25	n-hexanol	102.18	2.03	9.71	1	1	0.0194	-1.71	full-thickness	abdomen	static	saline	not available	0.5	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
26	n-hexanol	102.18	2.03	9.71	1	1	0.0286	-1.54	full-thickness	abdomen	static	saline	not available	5	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
27	n-hexanol	102.18	2.03	9.71	1	1	0.0386	-1.41	full-thickness	abdomen	static	saline	not available	10	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
28	n-hexanol	102.18	2.03	9.71	1	1	0.0374	-1.43	full-thickness	abdomen	static	saline	not available	15	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
29	n-hexanol	102.18	2.03	9.71	1	1	0.0374	-1.43	full-thickness	abdomen	static	saline	not available	20	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
30	n-hexanol	102.18	2.03	9.71	1	1	0.00381	-2.42	full-thickness	abdomen	static	saline	not available	28	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
31	n-heptanol	116.2	1.82	9.57	1	1	0.0659	-1.18	full-thickness	abdomen	static	saline	not available	0.5	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
32	n-heptanol	116.2	1.82	9.57	1	1	0.0807	-1.09	full-thickness	abdomen	static	saline	not available	5	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
33	n-heptanol	116.2	1.82	9.57	1	1	0.1014	-0.99	full-thickness	abdomen	static	saline	not available	10	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
34	n-heptanol	116.2	1.82	9.57	1	1	0.0979	-1.01	full-thickness	abdomen	static	saline	not available	15	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
35	n-heptanol	116.2	1.82	9.57	1	1	0.1026	-0.98	full-thickness	abdomen	static	saline	not available	20	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
36	n-heptanol	116.2	1.82	9.57	1	1	0.1015	-0.99	full-thickness	abdomen	static	saline	not available	25	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
37	hydrocortisone	362.5	1.62	12.75	5	3	0.0001	-4.00	full-thickness	abdomen	static	saline	37	40	radiolabelled (3H)	*J.Pharm.Sci.*73:1287-1290

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
38	hydrocortisone	362.5	1.62	12.75	5	3	0.00006	-4.22	full-thickness	abdomen	static	40% aq. PEG 400	37	not available	HPLC	*J.Pharm.Sci.*76:123-126
39	17a-hydroxyprogesterone	330.5	3.08	10.98	3	1	0.00087	-3.06	full-thickness	abdomen	static	40% aq. PEG 400	37	not available	HPLC	*J.Pharm.Sci.*76:123-126
40	methanol	32.04	-0.63	11.68	1	1	0.0018	-2.74	full-thickness	abdomen / dorsal	static	saline	not available	0.3	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
41	methanol	32.04	-0.63	11.68	1	1	0.0016	-2.80	full-thickness	abdomen / dorsal	static	saline	not available	5.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
42	methanol	32.04	-0.63	11.68	1	1	0.0017	-2.77	full-thickness	abdomen / dorsal	static	saline	not available	9.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
43	methanol	32.04	-0.63	11.68	1	1	0.0019	-2.72	full-thickness	abdomen / dorsal	static	saline	not available	13.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
44	methanol	32.04	-0.63	11.68	1	1	0.0018	-2.74	full-thickness	abdomen / dorsal	static	saline	not available	17.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
45	methanol	32.04	-0.63	11.68	1	1	0.0018	-2.74	full-thickness	abdomen / dorsal	static	saline	not available	26.3	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
46	methanol	32.04	-0.63	11.68	1	1	0.001	-3.00	full-thickness	abdomen	static	saline	not available	2	radiolabelled (3H)	*J.Soc.Cosmet.Chem.*, 35:237-252
47	morphine	285.3	0.72	13.68	4	2	0.00015	-3.82	full-thickness	dorsal / abdominal	flow-through	isotonic phosphate buffer & sodium azide	37	9	HPLC	*Int.J.Pharm.*, 299:131-137
48	nicorandil	211.18	0.43	14.40	3	1	0.001008	-3.00	full-thickness	abdomen	static	saline	37	32	HPLC	*J.Pharm.Sci*,80:104-107
49	n-octanol	130.23	2.81	9.45	1	1	0.0782	-1.11	full-thickness	abdomen / dorsal	static	saline	not available	0.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75:346-352
50	n-octanol	130.23	2.81	9.45	1	1	0.1208	-0.92	full-thickness	abdomen / dorsal	static	saline	not available	6.2	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75:346-352
51	n-octanol	130.23	2.81	9.45	1	1	0.0945	-1.02	full-thickness	abdomen / dorsal	static	saline	not available	10	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75:346-352
52	n-octanol	130.23	2.81	9.45	1	1	0.0931	-1.03	full-thickness	abdomen / dorsal	static	saline	not available	15	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75:346-352
53	n-octanol	130.23	2.81	9.45	1	1	0.0948	-1.02	full-thickness	abdomen / dorsal	static	saline	not available	22	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75:346-352
54	n-octanol	130.23	2.81	9.45	1	1	0.097	-1.01	full-thickness	abdomen / dorsal	static	saline	not available	27	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75:346-352
55	prednisolone 21-heptanoate	472.62	4.6	12.02	5	2	0.000077	-4.11	not available	abdomen	not available	ethanol & water (8:2)	25 (not available)	48	HPLC	*Int.J.Pharm.*, 158:11-18
56	prednisolone 21-octanoate	486.65	5.09	11.89	5	2	0.00011	-3.96	not available	abdomen	not available	ethanol & water (8:2)	25 (not available)	48	HPLC	*Int.J.Pharm.*, 158:11-18
57	prednisolone 21-nonanoate	500.68	5.58	11.78	5	2	0.000092	-4.04	not available	abdomen	not available	ethanol & water (8:2)	25 (not available)	48	HPLC	*Int.J.Pharm.*, 158:11-18
58	prednisolone 21-decanoate	514.7	6.07	11.67	5	2	0.000111	-3.95	not available	abdomen	not available	ethanol & water (8:2)	25 (not available)	48	HPLC	*Int.J.Pharm.*, 158:11-18
59	prednisolone 21-undecanoate	528.73	5.54	11.57	5	2	0.000149	-3.83	not available	abdomen	not available	ethanol & water (8:2)	25 (not available)	48	HPLC	*Int.J.Pharm.*, 158:11-18
60	prednisolone 21-tridecanoate	556.78	6.02	11.39	5	2	0.000106	-3.97	not available	abdomen	not available	ethanol & water (8:2)	25 (not available)	48	HPLC	*Int.J.Pharm.*, 158:11-18
61	prednisolone 21-pentadecanoate	584.84	6.79	11.23	5	2	0.000098	-4.01	not available	abdomen	not available	ethanol & water (8:2)	25 (not available)	48	HPLC	*Int.J.Pharm.*, 158:11-18
62	progesterone	314.5	3.67	10.05	2	0	0.011	-1.96	full-thickness	abdomen	static	40% aq. PEG 400	37	not available	HPLC	*J.Pharm.Sci.*,76:123-126
63	propranolol HCL	295	0.74	11.96	3	2	0.00005	-4.30	full-thickness	abdomen	flow-through	dist. water	37	not available	HPLC	*J.Pharm.Sci*, 86:1369-1372
64	thiourea	76.12	-1.31	15.23	0	2	9.60E-05	-4.02	full-thickness	abdomen	static	saline	37	6	radiolabelled (^{14}C)	*Int.J.Pharm.*,36: 61-66
65	water	18.02	-1.38	26.68	1	1	0.0016	-2.80	full-thickness	abdomen / dorsal	static	saline	not available	0.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
66	water	18.02	-1.38	26.68	1	1	0.0015	-2.82	full-thickness	abdomen / dorsal	static	saline	not available	5.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
67	water	18.02	-1.38	26.68	1	1	0.0014	-2.85	full-thickness	abdomen / dorsal	static	saline	not available	10.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
68	water	18.02	-1.38	26.68	1	1	0.0013	-2.89	full-thickness	abdomen / dorsal	static	saline	not available	15.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
69	water	18.02	-1.38	26.68	1	1	0.0012	-2.92	full-thickness	abdomen / dorsal	static	saline	not available	25.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
70	water	18.02	-1.38	26.68	1	1	1.10E-05	-4.96	full-thickness	abdomen / dorsal	static	saline	not available	29.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
71	water	18.02	-1.38	26.68	1	1	1.90E-03	-2.72	full-thickness	abdomen	static	saline	not available	2	radiolabelled (3H)	*J.Soc.Cosmet.Chem.*,35:237-252
72	ondasetron	293.36	2.3	9.83	2	0	0.00133518		full-thickness	abdomen	static	40% PEG 400 in saline	37	30	HPLC	*Drug Development and Technology*: vol.9, 63-74, 2010

Group C3

Type of skin: mouse | Site: dorsal | Cell type: flow through / static cells | Temperature: any | Time: any | HPLC / GC / radiolabelled | Vehicle: any | Receptor fluid: any

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	alachlor	269.77	3.37	9.80	2	0	0.000377	-3.42	full-thickness	dorsal	flow-through	Hanks balanced saline solution & 4% BSA	not available	24	radiolabelled (^{14}C)	*Toxicol.Sci.*, 68:18-23
2	alachlor	269.77	3.37	9.80	2	0	0.000655	-3.18	full-thickness	dorsal	flow-through	Hanks balanced saline solution & 4% BSA	not available	24	radiolabelled (^{14}C)	*Toxicol.Sci.*, 68:18-23
3	atenolol	266.3	-0.03	12.49	4	3	0.0479	-1.32	full-thickness	dorsal	flow-through	0,1 % sodium azide solution in dist. water	37	24	UV / spectroscopy	*Ind.J.Exp.Biol.*. 31:691-693
4	atenolol	266.3	-0.03	12.49	4	3	0.025	-1.60	full-thickness	dorsal	flow-through	0.1 % sodium azide solution in dist. water	37	24	UV / spectroscopy	*Ind.J.Exp.Biol.*, 31:691-693
5	atenolol	266.3	-0.03	12.49	4	3	0.0213	-1.67	full-thickness	dorsal	flow-through	0.1 % sodium azide solution in dist. water	37	24	UV / spectroscopy	*Ind.J.Exp.Biol.*, 31:691-693
6	atrazine	215.69	2.82	11.77	5	2	0.000769	-3.11	full-thickness	dorsal	flow-through	Hanks balanced saline solution & 4% BSA	not available	24	radiolabelled (^{14}C)	*Toxicol.Sci.*, 68:18-23
7	atrazine	215.69	2.82	11.77	5	2	0.000168	-3.77	full-thickness	dorsal	flow-through	Hanks balanced saline solution & 4% BSA	not available	24	radiolabelled (^{14}C)	*Toxicol.Sci.*, 68:18-23
8	bisphenol A diglycidyl ether (BADGE)	340.8	3.84	10.38	4	0	0.0000085	-5.07	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	not available	24	radiolabelled (^{14}C)	*Xenobiotica*, 30:469-483
9	n-butanol	74.14	0.84	10.13	1	1	0.0065	-2.19	full-thickness	abdomen / dorsal	static	saline	not available	0.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
10	n-butanol	74.14	0.84	10.13	1	1	0.0082	-2.09	full-thickness	abdomen / dorsal	static	saline	not available	4.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
11	n-butanol	74.14	0.84	10.13	1	1	0.0118	-1.93	full-thickness	abdomen / dorsal	static	saline	not available	7.8	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
12	n-butanol	74.14	0.84	10.13	1	1	0.0124	-1.91	full-thickness	abdomen / dorsal	static	saline	not available	11.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
13	n-butanol	74.14	0.84	10.13	1	1	0.0119	-1.92	full-thickness	abdomen / dorsal	static	saline	not available	14.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
14	n-butanol	74.14	0.84	10.13	1	1	0.0115	-1.94	full-thickness	abdomen / dorsal	static	saline	not available	26.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
15	caffeine	194.2	0.16	32.83	4	0	0.00026	-3.59	full-thickness	dorsal / abdominal	static	isotonic phosphate buffer & sodium azide	37	9	HPLC	*J.Cont.Release*, 33:71-77
16	coumarin	146.15	1.51	11.91	1	0	0.001	-3.00	full-thickness	dorsal	flow-through	HBSS, HEPES & 0.5% gentamycin	32 (skin)	72	radiolabelled (^{14}C)	*Toxicol.Appl.Pharmacol.*, 145:34-42
17	o-cresyl glycidyl ether (oCGE)	164.20	2.16	10.38	2	0	0.000176	-3.75	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (^{14}C)	*Xenobiotica*, 30:469-483

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
18	decabromodiphenyl oxide (DBDPO)	959.17	12.11	8.10	1	0	0.00000117	-5.93	full-thickness	dorsal	flow-through	HEPES-buffered HBSS & 10% FBS	not available	24	radiolabelled (^{14}C)	*Food Chem.Toxicol.,* 39:1263
19	decabromodiphenyl oxide (DBDPO)	959.17	12.11	8.10	1	0	0.00000164	-5.79	full-thickness	dorsal	flow-through	HEPES-buffered HBSS & 10% FBS	not available	24	radiolabelled (^{14}C)	*Food Chem.Toxicol.,* 39:1263
20	decabromodiphenyl oxide (DBDPO)	959.17	12.11	8.10	1	0	0.00000703	-5.15	full-thickness	dorsal	flow-through	HEPES-buffered HBSS & 10% FBS	not available	24	radiolabelled (^{14}C)	*Food Chem.Toxicol.,* 39:1263
21	dodecyl glycidyl ether (C12GE)	242.2	5.01	8.41	2	0	4.61E-05	-4.34	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (^{14}C)	*Xenobiotica,* 30:469-483
22	ethanol	46.07	-0.14	10.92	1	1	0.0021	-2.68	full-thickness	abdomen / dorsal	static	saline	not available	0.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.,*75:346-352
23	ethanol	46.07	-0.14	10.92	1	1	0.0022	-2.66	full-thickness	abdomen / dorsal	static	saline	not available	5.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.,*75:346-352
24	ethanol	46.07	-0.14	10.92	1	1	0.0023	-2.64	full-thickness	abdomen / dorsal	static	saline	not available	10.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.,*75:346-352
25	ethanol	46.07	-0.14	10.92	1	1	0.0022	2.66	full-thickness	abdomen / dorsal	static	saline	not available	15.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.,*75:346-352
26	ethanol	46.07	-0.14	10.92	1	1	0.0021	-2.68	full-thickness	abdomen / dorsal	static	saline	not available	20.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.,*75:346-352
27	ethanol	46.07	-0.14	10.92	1	1	0.002	-2.70	full-thickness	abdomen / dorsal	static	saline	not available	25.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.,*75:346-352
28	ethanol	46.07	-0.14	10.92	1	1	0.0019	-2.72	full-thickness	abdomen / dorsal	static	saline	not available	29.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.,*75:346-352
29	epikote YX4000	354.4	5.19	11.00	4	0	2.63 E -06	-5.58	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (^{14}C)	*Xenobiotica,* 30:469-483
30	etorphine	411.55	3.02	11.76	5	2	0.0046	-2.34	full-thickness	abdominal/dorsal	static	isotonic tris buffer	37	24	radiolabelled (3H)	*Pharmaceut.Res.,* 9:963-965
31	1,6-hexanediol diglycidyl ether (HDDGE)	230.2	0.84	9.36	4	0	5.77 E -04	-3.24	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (^{14}C)	*Xenobiotica,* 30:469-483
32	hydrocortisone	362.5	1.62	12.75	5	3	0.00012	-3.92	full-thickness	dorsal	static	saline	37	40	radiolabelled (3H)	*J.Pharm.Sci.*73:1287-1290
33	lidocaine	234.34	1.66	8.78	2	1	0.0089	-2.05	full-thickness	dorsal / ventral	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (^{14}C)	*Int.J.Pharm.*71:167-173
34	lidocaine	234.34	1.66	8.78	2	1	0.0176	-1.75	full-thickness	dorsal / ventral	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (^{14}C)	*Int.J.Pharm.*71:167-173
35	lidocaine	234.34	1.66	8.78	2	1	0.018	-1.74	full-thickness	dorsal / ventral	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (^{14}C)	*Int.J.Pharm.*71:167-173
36	lidocaine	234.34	1.66	8.78	2	1	0.026	-1.59	full-thickness	dorsal / ventral	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (^{14}C)	*Int.J.Pharm.*71:167-173
37	methanol	32.04	-0.63	11.68	1	1	0.0018	-2.74	full-thickness	abdomen / dorsal	static	saline	not available	0.3	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
38	methanol	32.04	-0.63	11.68	1	1	0.0016	-2.80	full-thickness	abdomen / dorsal	static	saline	not available	5.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
39	methanol	32.04	-0.63	11.68	1	1	0.0017	-2.77	full-thickness	abdomen / dorsal	static	saline	not available	9.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
40	methanol	32.04	-0.63	11.68	1	1	0.0019	-2.72	full-thickness	abdomen / dorsal	static	saline	not available	13.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
41	methanol	32.04	-0.63	11.68	1	1	0.0018	-2.74	full-thickness	abdomen / dorsal	static	saline	not available	17.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
42	methanol	32.04	-0.63	11.68	1	1	0.0018	-2.74	full-thickness	abdomen / dorsal	static	saline	not available	26.3	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
43	morphine	285.3	0.72	13.68	4	2	0.00015	-3.82	full-thickness	dorsal / abdominal	flow-through	isotonic phosphate buffer & sodium azide	37	9	HPLC	*Int.J.Pharm.*, 299:131-137
44	n-octanol	130.23	2.81	9.45	1	1	0.0782	-1.11	full-thickness	abdomen / dorsal	static	saline	not available	0.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75:346-352
45	n-octanol	130.23	2.81	9.45	1	1	0.1208	-0.92	full-thickness	abdomen / dorsal	static	saline	not available	6.2	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75:346-352

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
46	n-octanol	130.23	2.81	9.45	1	1	0.0945	-1.02	full-thickness	abdomen / dorsal	static	saline	not available	10	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75:346-352
47	n-octanol	130.23	2.81	9.45	1	1	0.0931	-1.03	full-thickness	abdomen / dorsal	static	saline	not available	15	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75:346-352
48	n-octanol	130.23	2.81	9.45	1	1	0.0948	-1.02	full-thickness	abdomen / dorsal	static	saline	not available	22	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75:346-352
49	n-octanol	130.23	2.81	9.45	1	1	0.097	-1.01	full-thickness	abdomen / dorsal	static	saline	not available	27	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75:346-352
50	salicylic acid	138.1	2.24	14.39	2	2	0.01954	-1.71	full-thickness	dorsal	static	tris HCL buffer sol.	25	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, ,45:414-418
51	salicylic acid	138.1	2.24	14.39	2	2	0.01162	-1.93	full-thickness	dorsal	static	tris HCL buffer sol.	25	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, ,45:414-418
52	salicylic acid	138.1	2.24	14.39	2	2	0.00074	-3.13	full-thickness	dorsal	static	tris HCL buffer sol.	25	72	fluorescence spectrophotometry	*J.Pharm.Pharmacol.*, ,45:414-418
53	TDCPP	430.91	3.65	8.67	1	0	0.00046	-3.34	full-thickness	dorsal	flow-through	HEPES-buffered, HBSS & 10% FBS	not available	24	radiolabelled (^{14}C)	*Food Chem.Toxicol.*,39:1263-1270
54	TDCPP	430.91	3.65	8.67	1	0	0.00056	-3.25	full-thickness	dorsal	flow-through	HEPES-buffered, HBSS &10% FBS	not available	24	radiolabelled (^{14}C)	*Food Chem.Toxicol.*,39:1263-1270
55	trifluralin	335.28	5.31	9.49	6	0	0.000279	-3.55	full-thickness	dorsal	flow-through	Hanks balanced saline solution & 4% BSA	not available	24	radiolabelled (^{14}C)	*Toxicol.Sci.,* 68:18-23
56	trifluralin	335.28	5.31	9.49	6	0	0.000122	-3.91	full-thickness	dorsal	flow-through	Hanks balanced saline solution & 4% BSA	not available	24	radiolabelled (^{14}C)	*Toxicol.Sci.,* 68:18-23
57	water	18.02	-1.38	26.68	1	1	0.00219	-2.66	full-thickness	dorsal	flow-through	0.002% sodium azide solution	31 (skin)	6	radiolabelled (3H)	*J.Investig.Dermatol.*, 94: 235-240
58	water	18.02	-1.38	26.68	1	1	0.0016	-2.80	full-thickness	abdomen / dorsal	static	saline	not available	0.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
59	water	18.02	-1.38	26.68	1	1	0.0015	-2.82	full-thickness	abdomen / dorsal	static	saline	not available	5.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
60	water	18.02	-1.38	26.68	1	1	0.0014	-2.85	full-thickness	abdomen / dorsal	static	saline	not available	10.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
61	water	18.02	-1.38	26.68	1	1	0.0013	-2.89	full-thickness	abdomen / dorsal	static	saline	not available	15.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
62	water	18.02	-1.38	26.68	1	1	0.0012	-2.92	full-thickness	abdomen / dorsal	static	saline	not available	25.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
63	water	18.02	-1.38	26.68	1	1	1.10E-05	-4.96	full-thickness	abdomen / dorsal	static	saline	not available	29.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
64	water	18.02	-1.38	26.68	1	1	1.80E-02	-1.74	not available	dorsal	flow-through	saline & unlabelled urea	37 (not available)	48	radiolabelled (3H)	*S.African J.Sci.*, 84 :440-441
65	water	18.02	-1.38	26.68	1	1	1.00E-02	-2.00	not available	dorsal	flow-through	saline & unlabelled urea	37 (not available)	12	radiolabelled (3H)	*S.African J.Sci.*, 84 :440-441
66	urea	60.6	-1.56	14.36	1	2	3.00E-04	-3.52	not available	dorsal	flow-through	saline & unlabelled urea	37 (not available)	6	radiolabelled (3H)	*S.African J.Sci.*, 84 :440-441
67	urea	60.6	-1.56	14.36	1	2	7.00E-04	-3.15	not available	dorsal	flow-through	saline & unlabelled urea	37 (not available)	12	radiolabelled (3H)	*S.African J.Sci.*, 84 :440-441

Group C4

Type of skin: mouse Site: any Cell type: flow through / static cells Temperature: 37 °C Time: any HPLC / GC / radiolabelled Vehicle: any Receptor fluid: any

No	Name	MW	Log P KOWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	atenolol	266.30	-0.03	12.49	4	3	0.05	-1.32	full-thickness	abdomen	flow-through	0.1% sodium azide solution in dist. water	37	24	UV spectroscopy	*Ind.J.Exp.Biol.*, 31: 691-693
2	atenolol	266.30	-0.03	12.49	4	3	0.05	-1.32	full-thickness	dorsal	flow-through	0.1% sodium azide solution in dist. water	37	24	UV spectroscopy	*Ind.J.Exp.Biol.*, 31: 691-693

No	Name	MW	Log P KOWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
3	atenolol	266.30	-0.03	12.49	4	3	0.03	-1.52	full-thickness	abdomen	flow-through	0.1% sodium azide solution in dist. water	37	24	UV spectroscopy	*Ind.J.Exp.Biol.*, 31: 691-693
4	atenolol	266.30	-0.03	12.49	4	3	0.03	-1.6	full-thickness	dorsal	flow-through	0.1% sodium azide solution in dist. water	37	24	UV spectroscopy	*Ind.J.Exp.Biol.*, 31: 691-693
5	atenolol	266.30	-0.03	12.49	4	3	0.04	-1.45	full-thickness	abdomen	flow-through	0.1% sodium azide solution in dist. water	37	24	UV spectroscopy	*Ind.J.Exp.Biol.*, 31: 691-693
6	atenolol	266.30	-0.03	12.49	4	3	0.02	-1.67	full-thickness	dorsal	flow-through	0.1% sodium azide solution in dist. water	37	24	UV spectroscopy	*Ind.J.Exp.Biol.*, 31: 691-693
7	caffeine	194.20	0.16	32.83	4	0	0.00026	-3.59	full-thickness	dorsal / abdominal	static	isotonic phosphate buffer & sodium azide	37	9	HPLC	*J.Cont.Release*, 33: 71-77
8	corticosterone	346.50	1.99	11.91	4	2	0.00053	-3.28	full-thickness	abdomen	static	40% aq. PEG 400	37	not available	HPLC	*J.Pharm.Sci.*, 76: 123-126
9	deoxycortisone	330.47	3.12	11.03	3	1	0.0034	-2.47	full-thickness	abdomen	static	40% aq. PEG 400	37	not available	HPLC	*J.Pharm.Sci.*, 76: 123-126
10	erioglaucine	793.86	-1.50	not calc.	not calc.	not calc.	0.00003	-4.52	full-thickness	abdomen	static	0.9% saline	37	24	spectrophotometry	*J.Pharm.Pharmacol.*, 42: 468-472
11	etorphine	411.55	3.02	11.76	5	2	0.0046	-2.34	full-thickness	abdominal / dorsal	static	isotonic tris buffer	37	24	radiolabelled (3H)	*Pharmaceut.Res.*, 9: 963-965
12	hydrocortisone	362.50	1.62	12.75	5	3	0.0001	-4	full-thickness	abdomen	static	saline	37	40	radiolabelled (3H)	*J.Pharm.Sci.*, 73: 1287-1290
13	hydrocortisone	362.50	1.62	12.75	5	3	0.00012	-3.92	full-thickness	dorsal	static	saline	37	40	radiolabelled (3H)	*J.Pharm.Sci.*, 73: 1287-1290
14	hydrocortisone	362.50	1.62	12.75	5	3	0.00006	-4.22	full-thickness	abdomen	static	40% aq. PEG 400	37	not available	HPLC	*J.Pharm.Sci.*, 76:123-126
15	17a-hydroxyprogesterone	330.50	3.08	10.98	3	1	0.00087	-3.06	full-thickness	abdomen	static	40% aq. PEG 400	37	not available	HPLC	*J.Pharm.Sci.*, 76: 123-126
16	lidocaine	234.34	1.66	8.78	2	1	0.0089	-2.05	full-thickness	dorsal / ventral	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (^{14}C)	*Int.J.Pharm.*, 71: 167-173
17	lidocaine	234.34	1.66	8.78	2	1	0.02	-1.75	full-thickness	dorsal / ventral	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (^{14}C)	*Int.J.Pharm.*, 71: 167-173
18	lidocaine	234.34	1.66	8.78	2	1	0.02	-1.74	full-thickness	dorsal / ventral	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (^{14}C)	*Int.J.Pharm.*, 71: 167-173
19	lidocaine	234.34	1.66	8.78	2	1	0.03	-1.59	full-thickness	dorsal / ventral	flow-through	saline & 0.25% chlorobutanol	37	not available	radiolabelled (^{14}C)	*Int.J.Pharm.*, 71: 167-173
20	N-N-diethyl m-toluamide	191.28	2.26	10.70	1	0	0.0035	-2.46	full-thickness	back	flow-through	sterile Ringer's solution, trizma, glucose & antibiotics	37	48	radiolabelled (^{14}C)	*Toxicol.Vitro*, 7: 167-176
21	morphine	285.30	0.72	13.68	4	2	0.00015	-3.82	full-thickness	dorsal / abdominal	flow-through	isotonic phosphate buffer & sodium azide	37	9	HPLC	*Int.J.Pharm.*, 299: 131-137
22	nicorandil	211.18	0.43	14.40	3	1	0.00101	-3	full-thickness	abdomen	static	saline	37	32	HPLC	*J.Pharm.Sci.*, 80: 104-107
23	progesterone	314.50	3.67	10.05	2	0	0.01	-1.96	full-thickness	abdomen	static	40% aq. PEG 400	37	not available	HPLC	*J.Pharm.Sci.*, 76: 123-126
24	propranolol HCL	295.30	0.74	11.96	3	2	0.00005	-4.3	full-thickness	abdomen	flow-through	dist,water	37	not available	HPLC	*J.Pharm.Sci.*, 86: 1369-1372
25	sucrose	342.30	-4.27	18.06	11	8	0.0022	-2.66	full-thickness	not available	flow-through	isotonic PBS	37	not available	radiolabelled (3H)	*J.Pharm.Sci.*, 90: 1242-1254
26	thiourea	76.12	-1.31	15.23	0	2	0.0001	-4.02	full-thickness	abdomen	static	saline	37	6	radiolabelled (^{14}C)	*Int.J.Pharm.*, 36: 61-66

Group C5

Type of skin: mouse Site: all sites Temperature was not available HPLC / GC / radiolabelled Vehicle: any Receptor fluid: any

Cell type: flow through / static cells

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	alachlor	269.77	3.37	9.80	2	0	0.000377	-3.42	full-thickness	dorsal	flow-through	Hanks balanced saline solution & 4% BSA	not available	24	radiolabelled (^{14}C)	*Toxicol.Sci.*, 68:18-23
2	alachor	269.77	3.37	9.80	2	0	0.000655	-3.18	full-thickness	dorsal	flow-through	Hanks balanced saline solution & 4% BSA	not available	24	radiolabelled (^{14}C)	*Toxicol.Sci.*, 68:18-23
3	atrazine	215.69	2.82	11.77	5	2	0.000769	-3.11	full-thickness	dorsal	flow-through	Hanks balanced saline solution & 4% BSA	not available	24	radiolabelled (^{14}C)	*Toxicol.Sci.*, 68:18-23
4	atrazine	215.69	2.82	11.77	5	2	0.000168	-3.77	full-thickness	dorsal	flow-through	Hanks balanced saline solution & 4% BSA	not available	24	radiolabelled (^{14}C)	*Toxicol.Sci.*, 68:18-23
5	bisphenol A diglycidyl ether (BADGE)	340.8	3.84	10.38	4	0	0.0000085	-5.07	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	not available	24	radiolabelled (^{14}C)	*Xenobiotica*, 30:469-483
6	n-butanol	74.14	0.84	10.13	1	1	0.0065	-2.19	full-thickness	abdomen / dorsal	static	saline	not available	0.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,75:346-352
7	n-butanol	74.14	0.84	10.13	1	1	0.0082	-2.09	full-thickness	abdomen / dorsal	static	saline	not available	4.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,75:346-352
8	n-butanol	74.14	0.84	10.13	1	1	0.0118	-1.93	full-thickness	abdomen / dorsal	static	saline	not available	7.8	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,75:346-352
9	n-butanol	74.14	0.84	10.13	1	1	0.0124	-1.91	full-thickness	abdomen / dorsal	static	saline	not available	11.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,75:346-352
10	n-butanol	74.14	0.84	10.13	1	1	0.0119	-1.92	full-thickness	abdomen / dorsal	static	saline	not available	14.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,75:346-352
11	n-butanol	74.14	0.84	10.13	1	1	0.0115	-1.94	full-thickness	abdomen / dorsal	static	saline	not available	26.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,75:346-352
12	n-butanol	74.14	0.84	10.13	1	1	0.0127	-1.90	full-thickness	abdomen	static	saline	not available	2	radiolabelled (^{14}C)	*J.Soc.Cosmet.*, 35:237-252
13	n-butanol	74.14	0.84	10.13	1	1	0.0237	-1.63	full-thickness	back	static	saline	not available	2	radiolabelled (^{14}C)	*J.Soc.Cosmet.*, 35:237-252
14	decabromodiphenyl oxide (DBDPO)	959.17	12.11	8.10	1	0	0.00000117	-5.93	full-thickness	dorsal	flow-through	HEPES-buffered HBSS & 10% FBS	not available	24	radiolabelled (^{14}C)	*Food Chem.Toxicol.*, 39:1263
15	decabromodiphenyl oxide (DBDPO)	959.17	12.11	8.10	1	0	0.00000164	-5.79	full-thickness	dorsal	flow-through	HEPES-buffered HBSS & 10% FBS	not available	24	radiolabelled (^{14}C)	*Food Chem.Toxicol.*, 39:1263
16	decabromodiphenyl oxide (DBDPO)	959.17	12.11	8.10	1	0	0.00000703	-5.15	full-thickness	dorsal	flow-through	HEPES-buffered HBSS & 10% FBS	not available	24	radiolabelled (^{14}C)	*Food Chem.Toxicol.*, 39:1263
17	dibutyl squarate	226.27	2.45	10.58	4	0	0.00085	-3.07	full-thickness	not available	static	not available	not available	48	UV / spectroscopy	*Arch.Dermatol.Res.*, 280:57-60
18	diethyl squarate	170.16	4.07	11.50	4	0	0.001	-3.00	full-thickness	not available	static	not available	not available	48	UV / spectroscopy	*Arch.Dermatol.Res.*, 280:57-60
19	ethanol	46.07	-0.14	10.92	1	1	0.0021	-2.68	full-thickness	abdomen / dorsal	static	saline	not available	0.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
20	ethanol	46.07	-0.14	10.92	1	1	0.0022	-2.66	full-thickness	abdomen / dorsal	static	saline	not available	5.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
21	ethanol	46.07	-0.14	10.92	1	1	0.0023	-2.64	full-thickness	abdomen / dorsal	static	saline	not available	10.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
22	ethanol	46.07	-0.14	10.92	1	1	0.0022	2.66	full-thickness	abdomen / dorsal	static	saline	not available	15.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
23	ethanol	46.07	-0.14	10.92	1	1	0.0021	-2.68	full-thickness	abdomen / dorsal	static	saline	not available	20.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
24	ethanol	46.07	-0.14	10.92	1	1	0.002	-2.70	full-thickness	abdomen / dorsal	static	saline	not available	25.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352
25	ethanol	46.07	-0.14	10.92	1	1	0.0019	-2.72	full-thickness	abdomen / dorsal	static	saline	not available	29.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*,, 75:346-352

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
26	ethanol	46.07	-0.14	10.92	1	1	0.0009	-3.05	full-thickness	abdomen	static	saline	not available	2	radiolabelled (^{14}C)	*J.Soc.Cosmet.*, 35:237-252
27	ethanol	46.07	-0.14	10.92	1	1	0.0024	-2.62	full-thickness	back	static	saline	not available	2	radiolabelled (^{14}C)	*J.Soc.Cosmet.*, 35:237-252
28	n-hexanol	102.18	2.03	9.71	1	1	0.0194	-1.71	full-thickness	abdomen	static	saline	not available	0.5	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
29	n-hexanol	102.18	2.03	9.71	1	1	0.0286	-1.54	full-thickness	abdomen	static	saline	not available	5	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
30	n-hexanol	102.18	2.03	9.71	1	1	0.0386	-1.41	full-thickness	abdomen	static	saline	not available	10	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
31	n-hexanol	102.18	2.03	9.71	1	1	0.0374	-1.43	full-thickness	abdomen	static	saline	not available	15	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
32	n-hexanol	102.18	2.03	9.71	1	1	0.0374	-1.43	full-thickness	abdomen	static	saline	not available	20	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
33	n-hexanol	102.18	2.03	9.71	1	1	0.00381	-2.42	full-thickness	abdomen	static	saline	not available	28	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
34	n-hexanol	102.18	2.03	9.71	1	1	0.0845	-1.07	full-thickness	back	static	saline	not available	2	radiolabelled (^{14}C)	*J.Soc.Cosmet.*, 35:237-252
35	n-heptanol	116.2	1.82	9.57	1	1	0.0659	-1.18	full-thickness	abdomen	static	saline	not available	0.5	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
36	n-heptanol	116.2	1.82	9.57	1	1	0.0807	-1.09	full-thickness	abdomen	static	saline	not available	5	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
37	n-heptanol	116.2	1.82	9.57	1	1	0.1014	-0.99	full-thickness	abdomen	static	saline	not available	10	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
38	n-heptanol	116.2	1.82	9.57	1	1	0.0979	-1.01	full-thickness	abdomen	static	saline	not available	15	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
39	n-heptanol	116.2	1.82	9.57	1	1	0.1026	-0.98	full-thickness	abdomen	static	saline	not available	20	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
40	n-heptanol	116.2	1.82	9.57	1	1	0.1015	-0.99	full-thickness	abdomen	static	saline	not available	25	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
41	methanol	32.04	-0.63	11.68	1	1	0.0018	-2.74	full-thickness	abdomen / dorsal	static	saline	not available	0.3	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
42	methanol	32.04	-0.63	11.68	1	1	0.0016	-2.80	full-thickness	abdomen / dorsal	static	saline	not available	5.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
43	methanol	32.04	-0.63	11.68	1	1	0.0017	-2.77	full-thickness	abdomen / dorsal	static	saline	not available	9.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
44	methanol	32.04	-0.63	11.68	1	1	0.0019	-2.72	full-thickness	abdomen / dorsal	static	saline	not available	13.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
45	methanol	32.04	-0.63	11.68	1	1	0.0018	-2.74	full-thickness	abdomen / dorsal	static	saline	not available	17.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
46	methanol	32.04	-0.63	11.68	1	1	0.0018	-2.74	full-thickness	abdomen / dorsal	static	saline	not available	26.3	radiolabelled (^{14}C)	*J.Investig.Dermatol.*, 75:346-352
47	methanol	32.04	-0.63	11.68	1	1	0.001	-3.00	full-thickness	abdomen	static	saline	not available	2	radiolabelled (3H)	*J.Soc.Cosmet.Chem.*, 35:237-252
48	n-octanol	130.23	2.81	9.45	1	1	0.0782	-1.11	full-thickness	abdomen / dorsal	static	saline	not available	0.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75:346-352
49	n-octanol	130.23	2.81	9.45	1	1	0.1208	-0.92	full-thickness	abdomen / dorsal	static	saline	not available	6.2	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75:346-352
50	n-octanol	130.23	2.81	9.45	1	1	0.0945	-1.02	full-thickness	abdomen / dorsal	static	saline	not available	10	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75:346-352
51	n-octanol	130.23	2.81	9.45	1	1	0.0931	-1.03	full-thickness	abdomen / dorsal	static	saline	not available	15	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75:346-352
52	n-octanol	130.23	2.81	9.45	1	1	0.0948	-1.02	full-thickness	abdomen / dorsal	static	saline	not available	22	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75:346-352
53	n-octanol	130.23	2.81	9.45	1	1	0.097	-1.01	full-thickness	abdomen / dorsal	static	saline	not available	27	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75:346-352

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
54	squaric acid	114.06	-0.44	20.47	4	2	0.0007	-3.15	full-thickness	abdomen	static	not available	not available	48	UV / spectroscopy	*Arch.Dermatol.Res.*, 280:57-60
55	TDCPP	430.91	3.65	8.67	1	0	0.00046	-3.34	full-thickness	dorsal	flow-through	HEPES-buffered, HBSS & 10% FBS	not available	24	radiolabelled (^{14}C)	*Food Chem.Toxicol.*,39:1263-1270
56	TDCPP	430.91	3.65	8.67	1	0	0.00056	-3.25	full-thickness	dorsal	flow-through	HEPES-buffered, HBSS &10% FBS	not available	24	radiolabelled (^{14}C)	*Food Chem.Toxicol.*,39:1263-1270
57	trifluralin	335.28	5.31	9.49	6	0	0.000279	-3.55	full-thickness	dorsal	flow-through	Hanks balanced saline solution & 4% BSA	not available	24	radiolabelled (^{14}C)	*Toxicol.Sci.,* 68:18-23
58	trifluralin	335.28	5.31	9.49	6	0	0.000122	-3.91	full-thickness	dorsal	flow-through	Hanks balanced saline solution & 4% BSA	not available	24	radiolabelled (^{14}C)	*Toxicol.Sci.,* 68:18-23
59	water	18.02	-1.38	26.68	1	1	0.0016	-2.80	full-thickness	abdomen / dorsal	static	saline	not available	0.5	radiolabelled (3H)	*J.Investig.Dermatol., 75:* 346-352
60	water	18.02	-1.38	26.68	1	1	0.0015	-2.82	full-thickness	abdomen / dorsal	static	saline	not available	5.5	radiolabelled (3H)	*J.Investig.Dermatol., 75:* 346-352
61	water	18.02	-1.38	26.68	1	1	0.0014	-2.85	full-thickness	abdomen / dorsal	static	saline	not available	10.5	radiolabelled (3H)	*J.Investig.Dermatol., 75:* 346-352
62	water	18.02	-1.38	26.68	1	1	0.0013	-2.89	full-thickness	abdomen / dorsal	static	saline	not available	15.5	radiolabelled (3H)	*J.Investig.Dermatol., 75:* 346-352
63	water	18.02	-1.38	26.68	1	1	0.0012	-2.92	full-thickness	abdomen / dorsal	static	saline	not available	25.5	radiolabelled (3H)	*J.Investig.Dermatol., 75:* 346-352
64	water	18.02	-1.38	26.68	1	1	1.10E-05	-4.96	full-thickness	abdomen / dorsal	static	saline	not available	29.5	radiolabelled (3H)	*J.Investig.Dermatol., 75:* 346-352
65	water	18.02	-1.38	26.68	1	1	1.90E-03	-2.72	full-thickness	abdomen	static	saline	not available	2	radiolabelled (3H)	*J.Soc.Cosmet.Chem.*,35:237-252
66	water	18.02	-1.38	26.68	1	1	2.00E-02	-1.70	full-thickness	back	static	saline	not available	2	radiolabelled (3H)	*J.Soc.Cosmet.Chem.*,35:237-252

Group C6

Type of skin: mouse Temperature: Any Time: Any Analytical method: Any Vehicle: Any Receptor fluid: Any

Cell type: any Site: all sites

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	alachlor	269.77	9.80	3.37	2	0	0.000377	-3.42	diluted acetone with water (1:10)	full-thickness	dorsal	flow-through	Hanks balanced salne solution & 4% BSA	not given	24	radiolabelled (^{14}C)	*Toxicol.Sci.*, 68: 18-23
2	alachlor	269.77	9.80	3.37	2	0	0.000655	-3.18	diluted acetone with water (1:40)	full-thickness	dorsal	flow-through	Hanks balanced salne solution & 4% BSA	not given	24	radiolabelled (^{14}C)	*Toxicol.Sci.*, 68: 18-23
3	atenolol	266.30	12.49	-0.03	4	3	0.048	-1.32	methanol	full-thickness	abdomen	flow-through	0.1 % sodium azide solution in dist.water	37	24	UV/spectroscopy	*Ind.J.Exp.Biol.*, 31: 691-693
4	atenolol	266.30	12.49	-0.03	4	3	0.0479	-1.32	methanol	full-thickness	dorsal	flow-through	0.1 % sodium azide solution in dist.water	37	24	UV/spectroscopy	*Ind.J.Exp.Biol.*, 31: 691-693
5	atenolol	266.30	12.49	-0.03	4	3	0.0301	-1.52	methanol	full-thickness	abdomen	flow-through	0.1 % sodium azide solution in dist.water	37	24	UV/spectroscopy	*Ind.J.Exp.Biol.*, 31: 691-693
6	atenolol	266.30	12.49	-0.03	4	3	0.025	-1.60	methanol	full-thickness	dorsal	flow-through	0.1 % sodium azide solution in dist.water	37	24	UV/spectroscopy	*Ind.J.Exp.Biol.*, 31: 691-693
7	atenolol	266.30	12.49	-0.03	4	3	0.0351	-1.45	methanol	full-thickness	abdomen	flow-through	0.1 % sodium azide solution in dist.water	37	24	UV/spectroscopy	*Ind.J.Exp.Biol.*, 31: 691-693
8	atenolol	266.3	12.49	-0.03	4	3	0.0213	-1.67	methanol	full-thickness	dorsal	flow-through	0.1 % sodium azide solution in dist.water	37	24	UV/spectroscopy	*Ind.J.Exp.Biol.*, 31: 691-693
9	atrazine	215.69	11.77	2.82	5	2	0.000769	-3.11	diluted methanol with water (1:10)	full-thickness	dorsal	flow-through	Hanks balanced salne solution & 4% BSA	not given	24	radiolabelled (^{14}C)	*Toxicol.Sci.*, 68: 18-23

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
10	atrazine	215.69	11.77	2.82	5	2	0.000168	-3.77	diluted methanol with water (1:40)	full-thickness	dorsal	flow-through	Hanks balanced salne solution & 4% BSA	not given	24	radiolabelled (^{14}C)	*Toxicol.Sci.*, 68: 18-23
11	bisphenol A diglycidyl ether (BADGE)	340.80	10.38	3.84	4	0	0.0000085	-5.07	acetone	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	not given	24	radiolabelled (^{14}C)	*Xenobiotica*, 30: 469-483
12	n-butanol	74.14	10.13	0.84	1	1	0.0065	-2.19	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	0.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*75: 346-352
13	n-butanol	74.14	10.13	0.84	1	1	0.0082	-2.09	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	4.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*75: 346-352
14	n-butanol	74.14	10.13	0.84	1	1	0.0118	-1.93	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	7.8	radiolabelled (^{14}C)	*J.Invest.Dermatol.*75: 346-352
15	n-butanol	74.14	10.13	0.84	1	1	0.0124	-1.91	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	11.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*75: 346-352
16	n-butanol	74.14	10.13	0.84	1	1	0.0119	-1.92	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	14.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*75: 346-352
17	n-butanol	74.14	10.13	0.84	1	1	0.0115	-1.94	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	26.3	radiolabelled (^{14}C)	*J.Invest.Dermatol.*75: 346-352
18	n-butanol	74.14	10.13	0.84	1	1	0.0127	-1.90	saline & (3H) methanol	full-thickness	abdomen	static	saline	not given	2	radiolabelled (^{14}C)	*J.Soc.Cosmet.*, 35: 237-252
19	n-butanol	74.14	10.13	0.84	1	1	0.0237	-1.63	saline & (3H) methanol	full-thickness	back	static	saline	not given	2	radiolabelled (^{14}C)	*J.Soc.Cosmet.*, 35: 237-252
20	caffeine	194.20	32.83	0.16	4	0	0.00026	-3.59	isotonic phosphate buffer	full-thickness	dorsal/abdominal	static	isotonic phosphate buffer & sodium azide	37	9	HPLC	*J.Cont.Release*,33: 71-77
21	corticosterone	346.50	11.91	1.99	4	2	0.00053	-3.28	40% aq. PEG 400	full-thickness	abdomen	static	40% aq. PEG 400	37	not given	HPLC	*J.Pharm.Sci.*76: 123-126
22	coumarin	146.15	11.91	1.51	1	0	0.001	-3.00	ethanol	full-thickness	dorsal	flow-through	HBSS, HEPES & 0.5% gentamycin	32 (skin)	72	radiolabelled (^{14}C)	*Toxicol.Appl.Pharmacol.*,145: 34-42
23	o-cresyl glycidyl ether (oCGE)	164.20	10.38	2.16	2	0	0.000176	-3.75	acetone	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (^{14}C)	*Xenobiotica*, 30: 469-483
24	decabromodiphenyl oxide (DBDPO)	959.17	12.11	8.10	1	0	0.00000117	-5.93	tetrahydrofuran	full-thickness	dorsal	flow-through	HEPES-buffered HBSS & 10% FBS	not given	24	radiolabelled (^{14}C)	*Food Chem.Toxicol.*,39: 1263
25	decabromodiphenyl oxide (DBDPO)	959.17	12.11	8.10	1	0	0.00000164	-5.79	tetrahydrofuran	full-thickness	dorsal	flow-through	HEPES-buffered HBSS & 10% FBS	not given	24	radiolabelled (^{14}C)	*Food Chem.Toxicol.*,39: 1263
26	decabromodiphenyl oxide (DBDPO)	959.17	12.11	8.10	1	0	0.00000703	-5.15	tetrahydrofuran	full-thickness	dorsal	flow-through	HEPES-buffered HBSS & 10% FBS	not given	24	radiolabelled (^{14}C)	*Food Chem.Toxicol.*,39: 1263
27	deoxycortisone	330.47	11.03	3.12	3	1	0.0034	-2.47	40% aq. PEG 400	full-thickness	abdomen	static	40% aq. PEG 400	37	not given	HPLC	*J.Pharm.Sci.*76: 123-126
28	dibutyl squarate	226.27	10.58	2.45	4	0	0.00085	-3.07	acetone	full-thickness	not given	static	not given	not given	48	UV/spectroscopy	*Arch.Dermatol.Res.* 280: 57-60
29	diethyl squarate	170.16	11.50	4.07	4	0	0.001	-3.00	acetone	full-thickness	not given	static	not given	not given	48	UV/spectroscopy	*Arch.Dermatol.Res.*280: 57-60
30	dodecyl glycidyl ether (C12GE)	242.20	8.41	5.01	2	0	4.61E-05	-4.34	acetone	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (^{14}C)	*Xenobiotica*, 30: 469-483
31	ethanol	46.07	10.92	-0.14	1	1	0.0021	-2.68	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	0.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*75: 346-352
32	ethanol	46.07	10.92	-0.14	1	1	0.0022	-2.66	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	5.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*75: 346-352
33	ethanol	46.07	10.92	-0.14	1	1	0.0023	-2.64	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	10.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*75: 346-352
34	ethanol	46.07	10.92	-0.14	1	1	0.0022	2.66	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	15.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*75: 346-352
35	ethanol	46.07	10.92	-0.14	1	1	0.0021	-2.68	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	20.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*75: 346-352
36	ethanol	46.07	10.92	-0.14	1	1	0.002	-2.70	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	25.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*75: 346-352

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
37	ethanol	46.07	10.92	-0.14	1	1	0.0019	-2.72	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	29.5	radiolabelled (^{14}C)	*J.Invest.Dermatol.*75: 346-352
38	ethanol	46.07	10.92	-0.14	1	1	0.0009	-3.05	saline & (3H) water	full-thickness	abdomen	static	saline	not given	2	radiolabelled (^{14}C)	*J.Soc.Cosmet.*, 35: 237-252
39	ethanol	46.07	10.92	-0.14	1	1	0.0024	-2.62	saline & (3H) water	full-thickness	back	static	saline	not given	2	radiolabelled (^{14}C)	*J.Soc.Cosmet.*, 35: 237-252
40	epikote YX4000	354.40	11.00	5.19	4	0	2,63 E -06	-5.58	acetone	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (^{14}C)	*Xenobiotica*, 30: 469-483
41	erioglaucine	793.86	not calc.	-1.50	not calc.	not calc.	0.00003	-4.52	40% propylene glycol & 10% N-methyl-2-pyrrolidone	full-thickness	abdomen	static	0.9% saline	37	24	Spectrophotometry	*J.Pharm.Pharmacol.*42: 468-472
42	etorphine	411.55	11.76	3.02	5	2	0.0046	-2.34	HCL & isotonic TRIS buffer	full-thickness	abdominal/dorsal	static	isotonic tris buffer	37	24	radiolabelled (3H)	*Pharmaceut.Res.*9: 963-965
43	5-fluorouracil	130.01	13.46	-0.81	3	2	0.0000603	-4.22	0.002% aq. sodium azide solution	dermatomed 0.42 mm	abdomen	flow-through	0.002% aq. sodium azide solution	31	24	radiolabelled (3H)	*J.Investig.Pharmacol.*, 94: 235-240
44	n-hexanol	102.18	9.71	2.03	1	1	0.0194	-1.71	0.9% saline	full-thickness	abdomen	static	saline	not given	0.5	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
45	n-hexanol	102.18	9.71	2.03	1	1	0.0286	-1.54	0.9% saline	full-thickness	abdomen	static	saline	not given	5	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
46	n-hexanol	102.18	9.71	2.03	1	1	0.0386	-1.41	0.9% saline	full-thickness	abdomen	static	saline	not given	10	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
47	n-hexanol	102.18	9.71	2.03	1	1	0.0374	-1.43	0.9% saline	full-thickness	abdomen	static	saline	not given	15	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
48	n-hexanol	102.18	9.71	2.03	1	1	0.0374	-1.43	0.9% saline	full-thickness	abdomen	static	saline	not given	20	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
49	n-hexanol	102.18	9.71	2.03	1	1	0.00381	-2.42	0.9% saline	full-thickness	abdomen	static	saline	not given	28	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
50	n-hexanol	102.18	9.71	2.03	1	1	0.0845	-1.07	saline & (3H)methanol	full-thickness	back	static	saline	not given	2	radiolabelled (^{14}C)	*J.Soc.Cosmet.*, 35: 237-252
51	1,6-hexanediol diglycidyl ether (HDDGE)	230.20	9.36	0.84	4	0	5,77 E -04	-3.24	acetone	full-thickness	dorsal	flow-through	HBSS, HEPES, BSA & gentamycin	32 (skin)	24	radiolabelled (^{14}C)	*Xenobiotica*, 30: 469-483
52	n-heptanol	116.20	9.57	1.82	1	1	0.0659	-1.18	0.9% saline	full-thickness	abdomen	static	saline	not given	0.5	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
53	n-heptanol	116.20	9.57	1.82	1	1	0.0807	-1.09	0.9% saline	full-thickness	abdomen	static	saline	not given	5	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
54	n-heptanol	116.20	9.57	1.82	1	1	0.1014	-0.99	0.9% saline	full-thickness	abdomen	static	saline	not given	10	radiolabelled (^{14}C)	*J.Investig.Dermatol..*, 75: 346-352
55	n-heptanol	116.20	9.57	1.82	1	1	0.0979	-1.01	0.9% saline	full-thickness	abdomen	static	saline	not given	15	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
56	n-heptanol	116.20	9.57	1.82	1	1	0.1026	-0.98	0.9% saline	full-thickness	abdomen	static	saline	not given	20	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
57	n-heptanol	116.20	9.57	1.82	1	1	0.1015	-0.99	0.9% saline	full-thickness	abdomen	static	saline	not given	25	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
58	hydrocortisone	362.50	12.75	1.62	5	3	0.0001	-4.00	saline	full-thickness	abdomen	static	saline	37	40	radiolabelled (3H)	*J.Pharm.Sci.*73: 1287-1290
59	hydrocortisone	362.50	12.75	1.62	5	3	0.00012	-3.92	saline	full-thickness	dorsal	static	saline	37	40	radiolabelled (3H)	*J.Pharm.Sci.*73: 1287-1290
60	hydrocortisone	362.50	12.75	1.62	5	3	0.00006	-4.22	40% aq. PEG 400	full-thickness	abdomen	static	40% aq. PEG 400	37	not given	HPLC	*J.Pharm.Sci.*76: 123-126
61	17a-hydroxyprogesterone	330.50	10.98	3.08	3	1	0.00087	-3.06	40% aq. PEG 400	full-thickness	abdomen	static	40% aq. PEG 400	37	not given	HPLC	*J.Pharm.Sci.*76: 123-126
62	lidocaine	234.34	8.78	1.66	2	1	0.0089	-2.05	40% propylene glycol & HCL	full-thickness	dorsal/ventral	flow-through	saline & 0.25% chlorobutanol	37	not given	radiolabelled (^{14}C)	*Int.J.Pharm.*71: 167-173
63	lidocaine	234.34	8.78	1.66	2	1	0.0176	-1.75	40% propylene glycol & HCL	full-thickness	dorsal/ventral	flow-through	saline & 0.25% chlorobutanol	37	not given	radiolabelled (^{14}C)	*Int.J.Pharm.*71: 167-173
64	lidocaine	234.34	8.78	1.66	2	1	0.018	-1.74	40% propylene glycol & NaOH	full-thickness	dorsal/ventral	flow-through	saline & 0.25% chlorobutanol	37	not given	radiolabelled (^{14}C)	*Int.J.Pharm.*71: 167-173

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
65	lidocaine	234.34	8.78	1.66	2	1	0.026	-1.59	40% propylene glycol & NaOH	full-thickness	dorsal/ventral	flow-through	saline & 0.25% chlorobutanol	37	not given	radiolabelled (^{14}C)	*Int.J.Pharm.*71: 167-173
66	N-N-diethyl m-toluamide	191.28	10.70	2.26	1	0	0.0035	-2.46	acetone	full-thickness	back	flow-through	sterile Ringer's solution, Trizma, glucose & antibiotics	37	48	radiolabelled (^{14}C)	*Toxicol.Vitro*, 7: 167-176
67	methanol	32.04	11.68	-0.63	1	1	0.0018	-2.74	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	0.3	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
68	methanol	32.04	11.68	-0.63	1	1	0.0016	-2.80	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	5.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
69	methanol	32.04	11.68	-0.63	1	1	0.0017	-2.77	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	9.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
70	methanol	32.04	11.68	-0.63	1	1	0.0019	-2.72	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	13.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
71	methanol	32.04	11.68	-0.63	1	1	0.0018	-2.74	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	17.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
72	methanol	32.04	11.68	-0.63	1	1	0.0018	-2.74	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	26.3	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
73	methanol	32.04	11.68	-0.63	1	1	0.001	-3.00	Saline & (^{14}C) alkanol	full-thickness	abdomen	static	saline	not given	2	radiolabelled (3H)	*J.Soc.Cosmet.Chem.*, 35: 237-252
74	morphine	285.30	13.68	0.72	4	2	0.00015	-3.82	isotonic phosphate buffer	full-thickness	dorsal/abdominal	flow-through	isotonic phosphate buffer & sodium azide	37	9	HPLC	*Int.J.Pharm.*299: 131-137
75	nicorandil	211.18	14.40	0.43	3	1	0.001008	-3.00	water	full-thickness	abdomen	static	saline	37	32	HPLC	*J.Pharm.Sci.*,80: 104-107
76	n-octanol	130.23	9.45	2.81	1	1	0.0782	-1.11	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	0.8	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
77	n-octanol	130.23	9.45	2.81	1	1	0.1208	-0.92	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	6.2	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
78	n-octanol	130.23	9.45	2.81	1	1	0.0945	-1.02	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	10	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
79	n-octanol	130.23	9.45	2.81	1	1	0.0931	-1.03	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	15	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
80	n-octanol	130.23	9.45	2.81	1	1	0.0948	-1.02	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	22	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
81	n-octanol	130.23	9.45	2.81	1	1	0.097	-1.01	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	27	radiolabelled (^{14}C)	*J.Investig.Dermatol.*,75: 346-352
82	prednisolone 21-heptanoate	472.62	12.02	4.6	5	2	0.000077	-4.11	DES / ethanol	not given	abdomen	not given	ethanol & water (8:2)	25 (not given)	48	HPLC	*Int.J.Pharm.*, 158: 11-18
83	prednisolone 21-octanoate	486.65	11.89	5.09	5	2	0.00011	-3.96	DES / ethanol	not given	abdomen	not given	ethanol & water (8:2)	25 (not given)	48	HPLC	*Int.J.Pharm.*, 158: 11-18
84	prednisolone 21-nonanoate	500.68	11.78	5.58	5	2	0.000092	-4.04	DES / ethanol	not given	abdomen	not given	ethanol & water (8:2)	25 (not given)	48	HPLC	*Int.J.Pharm.*, 158: 11-18
85	prednisolone 21-decanoate	514.70	11.67	6.07	5	2	0.000111	-3.95	DES / ethanol	not given	abdomen	not given	ethanol & water (8:2)	25 (not given)	48	HPLC	*Int.J.Pharm.*, 158: 11-18
86	prednisolone 21-undecanoate	528.73	11.57	5.54	5	2	0.000149	-3.83	DES / ethanol	not given	abdomen	not given	ethanol & water (8:2)	25 (not given)	48	HPLC	*Int.J.Pharm.*, 158: 11-18
87	prednisolone 21-tridecanoate	556.78	11.39	6.02	5	2	0.000106	-3.97	DES / ethanol	not given	abdomen	not given	ethanol & water (8:2)	25 (not given)	48	HPLC	*Int.J.Pharm.*, 158: 11-18
88	prednisolone 21-pentadecanoate	584.84	11.23	6.79	5	2	0.000098	-4.01	DES / ethanol	not given	abdomen	not given	ethanol & water (8:2)	25 (not given)	48	HPLC	*Int.J.Pharm.*, 158: 11-18
89	progesterone	314.50	10.05	3.67	2	0	0.011	-1.96	40% aq. PEG 400	full-thickness	abdomen	static	40% aq. PEG 400	37	not given	HPLC	*J.Pharm.Sci.*,76: 123-126
90	propranolol HCL	295.00	11.96	0.74	3	2	0.00005	-4.30	hydroalcoholic mixture	full-thickness	abdomen	flow-through	dist,water	37	not given	HPLC	*J.Pharm.Sci.*, 86: 1369-1372
91	salicylic acid	138.10	14.39	2.24	2	2	0.01954	-1.71	phosphate buffer	full-thickness	dorsal	static	tris HCL buffer sol.	25	72	Fluorescence, spectrophotometry	*J.Pharm.Pharmacol.*,45: 414-418

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
92	salicylic acid	138.10	14.39	2.24	2	2	0.01162	-1.93	citric acid phosphate	full-thickness	dorsal	static	tris HCL buffer sol.	25	72	Fluorescence, spectrophotometry	*J.Pharm.Pharmacol.*,45: 414-418
93	salicylic acid	138.10	14.39	2.24	2	2	0.00074	-3.13	citric acid phosphate	full-thickness	dorsal	static	tris HCL buffer sol.	25	72	Fluorescence, spectrophotometry	*J.Pharm.Pharmacol.*,45: 414-418
94	squaric acid	114.06	20.47	-0.44	4	2	0.0007	-3.15	acetone	full-thickness	not given	static	not given	not given	48	UV/spectroscopy	*Arch.Dermatol.Res.*280: 57-60
95	sucrose	342.30	18.06	-4.27	11	8	0.0022	-2.66	NS	full-thickness	not given	flow-through	isotonic PBS	37	not given	radiolabelled (3H)	*J.Pharm.Sci.*, 90: 1242-1254
96	thiourea	76.12	15.23	-1.31	0	2	9.60E-05	-4.02	ethanol	full-thickness	abdomen	static	saline	37	6	radiolabelled (^{14}C)	*Int.J.Pharm.*,36: 61-66
97	TDCPP	430.91	8.67	3.65	1	0	0.00046	-3.34	acetone	full-thickness	dorsal	flow-through	HEPES-buffered, HBSS & 10% FBS	not given	24	radiolabelled (^{14}C)	*Food Chem.Toxicol.*,39: 1263-1270
98	TDCPP	430.91	8.67	3.65	1	0	0.00056	-3.25	acetone	full-thickness	dorsal	flow-through	HEPES-buffered, HBSS &10% FBS	not given	24	radiolabelled (^{14}C)	*Food Chem.Toxicol.*,39: 1263-1270
99	trifluralin	335.28	9.49	5.31	6	0	0.000279	-3.55	diluted acetone with water (1:10)	full-thickness	dorsal	flow-through	Hanks balanced salne solution & 4% BSA	not given	24	radiolabelled (^{14}C)	*Toxicol.Sci*, 68: 18-23
100	trifluralin	335.28	9.49	5.31	6	0	0.000122	-3.91	diluted acetone with water (1:40)	full-thickness	dorsal	flow-through	Hanks balanced salne solution & 4% BSA	not given	24	radiolabelled (^{14}C)	*Toxicol.Sci*, 68: 18-23
101	water	18.02	26.68	-1.38	1	1	0.00219	-2.66	none	full-thickness	dorsal	flow-through	0.002% sodium azide solution	31 (skin)	6	radiolabelled (3H)	*J.Investig.Dermatol.*, 94: 235-240
102	water	18.02	26.68	-1.38	1	1	0.0016	-2.80	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	0.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
103	water	18.02	26.68	-1.38	1	1	0.0015	-2.82	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	5.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
104	water	18.02	26.68	-1.38	1	1	0.0014	-2.85	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	10.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
105	water	18.02	26.68	-1.38	1	1	0.0013	-2.89	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	15.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
106	water	18.02	26.68	-1.38	1	1	0.0012	-2.92	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	25.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
107	water	18.02	26.68	-1.38	1	1	1.10E-05	-4.96	0.9% saline	full-thickness	abdomen/dorsal	static	saline	not given	29.5	radiolabelled (3H)	*J.Investig.Dermatol.*, 75: 346-352
108	water	18.02	26.68	-1.38	1	1	2.95E-03	-2.53	none	full-thickness	not given	flow-through	PBS	35 (skin)	48	radiolabelled (3H)	*J.Investig.Dermatol.*, 93: 87-91
109	water	18.02	26.68	-1.38	1	1	1.90E-03	-2.72	saline (^{14}C) ethanol	full-thickness	abdomen	static	saline	not given	2	radiolabelled (3H)	*J.Soc.Cosmet.Chem.*,35: 237-252
110	water	18.02	26.68	-1.38	1	1	2.00E-02	-1.70	saline (^{14}C) ethanol	full-thickness	back	static	saline	not given	2	radiolabelled (3H)	*J.Soc.Cosmet.Chem.*,35: 237-252
111	water	18.02	26.68	-1.38	1	1	1.80E-02	-1.74	aq. urea	not given	dorsal	flow-through	saline & unlabelled urea	37 (not given)	48	radiolabelled (3H)	*S. African J. Sci.*, 84: 440-441
112	water	18.02	26.68	-1.38	1	1	1.00E-02	-2.00	aq. urea	not given	dorsal	flow-through	saline & unlabelled urea	37 (not given)	12	radiolabelled (3H)	*S. African J. Sci.*, 84: 440-441
113	urea	60.60	14.36	-1.56	1	2	3.00E-04	-3.52	water	not given	dorsal	flow-through	saline & unlabelled urea	37 (not given)	6	radiolabelled (3H)	*S. African J. Sci.*, 84: 440-441
114	urea	60.60	14.36	-1.56	1	2	7.00E-04	-3.15	water	not given	dorsal	flow-through	saline & unlabelled urea	37 (not given)	12	radiolabelled (3H)	*S. African J. Sci.*, 84: 440-441

Appendix 8. Pig skin dataset (Group D)

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	atropine	289.38	1.91	11.04	3	1	1.76E-06	-5.75	isotonic phosphate buffered saline (pH7.4) with ethanol, propylene glycol, azone	epidermal membrane	pig ears	flow-through	PBS-buffer	37	24	radiolabelled (3H)	Bosman 1996
2	mannitol	182.17	-3.01	18.63	6	6	0.00152	-2.82	dist. water	isol.epidermis	outer ear	flow-through	physiological saline	32	not available	radiolabelled (14C)	*Toxicol.Vitro* 8: 827-830
3	2-phenylphenol	170.21	3.28	12.24	1	1	0.0159	-1.80	60% aq. ethanol	full-thickness	ear	perfused pig ear	oxygenated and filtered blood	30	4	radiolabelled (14C)	*Reg.Toxicol.Pharmacol.*, 35: 198-208
4	salicylic acid	138.10	2.24	14.39	2	2	1.27	0.10	90% aq. propylene glycol	dermatomed 0.6 mm	unknown	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215: 51-56
5	scopolamine	303.40	0.39	11.53	4	1	5.1E-07	-6.29	isotonic phosphate buffered saline (pH7.4) with ethanol, propylene glycol, azone	epidermal membrane	pig ears	flow-through	PBS-buffer	37	24	radiolabelled (3H)	Bosman 1996
6	terbinafine	291.4	5.81	9.33	1	0	0.001	-3.00	propylene glycol	dermatomed 0.6 mm	unknown	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215: 51-56
7	tropicamide	284.40	1.19	12.53	3	1	7E-07	-6.15	isotonic phosphate buffered saline (pH7.4) with ethanol, propylene glycol, azone	epidermal membrane	pig ears	flow-through	PBS-buffer	37	24	radiolabelled (3H)	Bosman 1996
8	water	18.02	-1.38	26.68	1	1	0.00225	-2.65	saline	full-thickness	outer ear	static	0.9% physiological saline	not available	not available	radiolabelled (3H)	*Toxicol.Vitro* 8: 827-830
9	caprtopril	217.29	0.84	11.55	2	2	0.000297	-3.53	aq. saturated sol.	fresh epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, vol.58: 167-177
10	caprtopril	217.29	0.84	11.55	2	2	0.00147	-2.83	aq. saturated sol.	frozen epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, vol.58: 167-177
11	methyl ester	231.29	2.9	9.31	2	0	0.001276	-2.75	aq. saturated sol.	fresh epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, vol.58: 167-177
12	methyl ester	231.29	2.9	9.31	2	0	0.00359	-2.44	aq. saturated sol.	frozen epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, vol.58: 167-177
13	ethyl ester	245.29	3.39	9.25	2	0	0.022	-1.66	aq. saturated sol.	fresh epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, vol.58: 167-177
14	ethyl ester	245.29	3.39	9.25	2	0	0.0081	-2.09	aq. saturated sol.	frozen epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, vol.58: 167-177
15	propyl ester	259	3.89	9.20	2	0	0.0158	-1.8	aq. saturated sol.	fresh epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, vol.58: 167-177
16	propyl ester	259	3.89	9.20	2	0	0.0122	-1.91	aq. saturated sol.	frozen epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, vol.58: 167-177
17	butyl ester	273.29	4.38	8.14	2	0	0.0146	-1.84	aq.saturated sol.	fresh epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, vol.58: 167-177
18	butyl ester	273.29	4.38	8.14	2	0	0.0108	-1.97	aq. saturated sol.	frozen epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, vol.58: 167-177
19	pentyl ester	287.29	4.87	9.11	2	0	0.00689	-2.16	aq. saturated sol.	fresh epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, vol.58: 167-177
20	pentyl ester	287.29	4.87	9.11	2	0	0.00108	-2.97	aq. saturated sol.	frozen epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, vol.58: 167-177
21	hexyl ester	301.29	5.36	9.07	2	0	0.00122	-2.91	aq. saturated sol.	frozen epidermal membrane	pig ears	static	phosphate buffered saline pH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, vol.58: 167-177
22	ligustrazine hydrochloride	136.1	2.18	10.24	2	0	0.000236	-3.63	enhancer sol. with ethanol	sc	back	static	water	32	24	HPLC	*Eur.J.Pharm.Biopharm.*, 2007
23	ligustrazine hydrochloride	136.1	2.18	10.24	2	0	0.000272	-3.57	enhancer sol. with azone	sc	back	static	water	32	24	HPLC	*Eur.J.Pharm.Biopharm.*, 2007
24	ligustrazine hydrochloride	136.1	2.18	10.24	2	0	0.00287	-2.54	enhancer sol. with cinnamic acid	sc	back	static	water	32	24	HPLC	*Eur.J.Pharm.Biopharm.*, 2007
25	ligustrazine hydrochloride	136.1	2.18	10.24	2	0	0.00173	-2.76	enhancer sol. with cinnamaldehyde	sc	back	static	water	32	24	HPLC	*Eur.J.Pharm.Biopharm.*, 2007
26	ligustrazine hydrochloride	136.1	2.18	10.24	2	0	0.00169	-2.77	enhancer sol. with cinnamic alcohol	sc	back	static	water	32	24	HPLC	*Eur.J.Pharm.Biopharm.*, 2007

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
27	cafeic acid	180.2	1.1	15.15	3	3	0.0016	-2.80	transcutol-propylene glycol	full-thickness	ears	static	isotonic saline solution, pH7	37	48	HPLC	*Int.J.Pharm.*, 331: 139-144
28	chlorogenic acid	354.3	-1	14.51	7	6	0.0024	-2.62	transcutol-propylene glycol	full-thickness	ears	static	isotonic saline solution, pH7	37	48	HPLC	*Int.J.Pharm.*, 331: 139-144
29	pentachlorophenol	266.33	5.12	10.78	1	1	0.00006	-4.22	ethanol	0.2-0.3 mm epidermal	dorsal	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007
30	pentachlorophenol	266.33	5.12	10.78	1	1	0.00037	-3.43	water	0.2-0.3 mm epidermal	dorsal	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007
31	pentachlorophenol	266.33	5.12	10.78	1	1	0.0048	-2.32	40% ethanol, 60% water	0.2-0.3 mm epidermal	dorsal	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007
32	pentachlorophenol	266.33	5.12	10.78	1	1	0.0065	-2.19	40% ethanol, 60% water, MNA	0.2-0.3 mm epidermal	dorsal	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007
33	pentachlorophenol	266.33	5.12	10.78	1	1	0.00009	-4.04	40% ethanol, 60% water, SLS	0.2-0.3 mm epidermal	dorsal	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007
34	ketoprofen	254.29	0.97	11.75	2	1	0.00021	-3.68	water	epidermal membrane	ears	static	PBS (7.4)	37	48	HPLC	*Skin Pharmacol.Physiol.*, 2010, 23: 113-116
35	ketoprofen	254.29	0.97	11.75	2	1	0.000312	-3.51	aloe vera	epidermal membrane	ears	static	PBS (7.4)	37	48	HPLC	*Skin Pharmacol.Physiol.*, 2010, 23: 113-116

Appendix 9. Membrane dataset (Group E)

No	Name	Skin	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
1	benzoic acid	test skin	122.1	1.87	11.94	1	1	0.086	-1.07	water	3 micron pore size polycarbonate membrane	N/A	static	LDE assay medium	32	24	radiolabelled (14C)	*Toxicol.Vitro* 6: 303-315
2	benzoic acid	test skin	122.1	1.87	11.94	1	1	0.0086	-2.07	water	3 micron pore size polycarbonate membrane	N/A	static	LDE assay medium	22	24	radiolabelled (14C)	*Toxicol.Vitro* 6: 303-315
3	benzoic acid	test skin	122.1	1.87	11.94	1	1	0.0067	-2.17	petrolatum	3 micron pore size polycarbonate membrane	N/A	static	LDE assay medium	32	24	radiolabelled (14C)	*Toxicol.Vitro* 6: 303-315
4	benzoic acid	test skin	122.1	1.87	11.94	1	1	0.0023	-2.64	petrolatum	3 micron pore size polycarbonate membrane	N/A	static	LDE assay medium	22	24	radiolabelled (14C)	*Toxicol.Vitro* 6: 303-315
5	caffeine	test skin	194.2	0.16	32.83	4	0	0.02	-1.70	water	3 micron pore size polycarbonate membrane	N/A	static	LDE assay medium	32	24	radiolabelled (14C)	*Toxicol.Vitro* 6: 303-315
6	caffeine	test skin	194.2	0.16	32.83	4	0	0.011	-1.96	water	3 micron pore size polycarbonate membrane	N/A	static	LDE assay medium	22	24	radiolabelled (14C)	*Toxicol.Vitro* 6: 303-315
7	caffeine	test skin	194.2	0.16	32.83	4	0	0.0024	-2.62	petrolatum	3 micron pore size polycarbonate membrane	N/A	static	LDE assay medium	32	24	radiolabelled (14C)	*Toxicol.Vitro* 6: 303-315
8	caffeine	test skin	194.2	0.16	32.83	4	0	0.0011	-2.96	petrolatum	3 micron pore size polycarbonate membrane	N/A	static	LDE assay medium	22	24	radiolabelled (14C)	*Toxicol.Vitro* 6: 303-315
9	clotrimazole	graftskin	344.85	6.26	11.17	2	0	2.04	0.31	propylene glycol	support membrane was removed	N/A	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215:51-56
10	clotrimazole	graftskin	344.85	6.26	11.17	2	0	1.88	0.27	propylene glycol	filter support was left attached	N/A	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215:51-56
11	DDT	testskin	354.5	6.79	9.45	0	0	0.007	-2.15	acetone	full-thickness	cultured human forehead	flow-through	Hanks HEPES buffered medium, BSA & gentamycin	37	48	radiolabelled (14C)	*Toxicol.Vitro* 8: 1219-1225
12	flufenamic acid	epiderm	281.2	4.88	10.96	5	2	0.002363	-2.62	wool alcohols ointment	pore size 0.00045 mm	N/A	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	J.Contr.Rel, 75:283-295
13	flufenamic acid	epiderm	281.2	4.88	10.96	5	2	0.003053	-2.51	wool alcohols ointment	pore size 0.00045 mm	N/A	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	J.Contr.Rel, 75:283-295
14	flufenamic acid	epiderm	281.2	4.88	10.96	5	2	0.002714	-2.57	wool alcohols ointment	pore size 0.00045 mm	N/A	flow-through	Sorensen's phosphate buffer (pH 7.4)	32	not available	HPLC	J.Contr.Rel, 75:283-295
15	salicylic acid	graftskin	138.1	2.24	14.39	2	2	4.55	0.66	90% aq. propylene glycol	support membrane was removed	N/A	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215:51-56
16	salicylic acid	skinethic	138.1	2.24	14.39	2	2	15.28	1.18	90% aq. propylene glycol	filter support was left attached	N/A	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215:51-56
17	terbinafine	graftskin	291.4	5.81	9.33	1	0	0.028	-1.56	propylene glycol	support membrane was removed	N/A	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215:51-56
18	terbinafine	skinethic	291.4	5.81	9.33	1	0	0.037	-1.43	propylene glycol	filter support was left attached	N/A	static	PBS / ethanol 3:1	32	48	RP HPLC	*Int.J.Pharm.*, 215:51-56
19	testosterone	testskin	288.4	3.27	10.66	2	1	0.029	-1.54	water	3 micron pore size polycarbonate membrane	N/A	static	LDE assay medium & gentamycin sulphate	32	6	radiolabelled (14C)	*Skin Pharmacol.*, 5:146-153
20	testosterone	testskin	288.4	3.27	10.66	2	1	0.014	-1.85	water	3 micron pore size polycarbonate membrane	N/A	static	LDE assay medium & gentamycin sulphate	22	6	radiolabelled (14C)	*Skin Pharmacol.*, 5:146-153
21	testosterone	not available	288.4	3.27	10.66	2	1	0.0007	-3.15	petrolatum	3 micron pore size polycarbonate membrane	N/A	static	LDE assay medium & gentamycin sulphate	22	6	radiolabelled (14C)	*Skin Pharmacol.*, 5:146-154
22	testosterone	not available	288.4	3.27	10.66	2	1	0.0016	-2.80	petrolatum	3 micron pore size polycarbonate membrane	N/A	static	LDE assay medium & gentamycin sulphate	32	6	radiolabelled (14C)	*Skin Pharmacol.*, 5:146-154
23	amethocaine	silastic	264.37	3.02	9.85	3	1	1.49E-06	-5.82	saturated solution of local anesthetic	5*10-3 cm thickness	N/A	static	saline	37	24	UV-spectroscopy	*Prediction of Perc.Penetration*, 1: 192-198

No	Name	Skin	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})	Vehicle	Membrane	Site	Cell type	Receptor fluid	Temp. (°C) water bath	Study duration (h)	Analytical technique	Journal
24	procaine	silastic	236.31	1.99	10.34	3	1	1.14E-07	-6.94	saturated solution of local anesthetic	5*10-3 cm thickness	N/A	static	saline	37	24	UV-spectroscopy	*Prediction of Perc.Penetration*, 1: 192-198
25	benzocaine	silastic	165.19	1.8	11.11	2	1	1.35E-06	-5.87	saturated solution of local anesthetic	5*10-3 cm thickness	N/A	static	saline	37	24	UV-spectroscopy	*Prediction of Perc.Penetration*, 1: 192-198
26	dibucaine	silastic	343.47	4.04	10.7	4	1	6.31E-07	-6.19	saturated solution of local anesthetic	5*10-3 cm thickness	N/A	static	saline	37	24	UV-spectroscopy	*Prediction of Perc.Penetration*, 1: 192-198
27	ketocaine	silastic	291.43	3.6	9.38	2	0	3.4E-07	-6.47	saturated solution of local anesthetic	5*10-3 cm thickness	N/A	static	saline	37	24	UV-spectroscopy	*Prediction of Perc.Penetration*, 1: 192-198
28	captopril	silastic	217.29	0.84	11.55	2	2	0.00394	-2.4	aq. saturated sol.	not available	N/A	static	phosphate buffered saline PH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
29	methyl ester	silastic	231.29	2.9	9.31	2	0	0.00488	-2.31	aq. saturated sol.	not available	N/A	static	phosphate buffered saline PH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
30	ethyl ester	silastic	245.29	3.39	9.25	2	0	0.00986	-2	aq. saturated sol.	not available	N/A	static	phosphate buffered saline PH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
31	propyl ester	silastic	259	3.89	9.20	2	0	0.0222	-1.65	aq. saturated sol.	not available	N/A	static	phosphate buffered saline PH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
32	butyl ester	silastic	273.29	4.38	8.14	2	0	0.0411	-1.39	aq. saturated sol.	not available	N/A	static	phosphate buffered saline PH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
33	pentyl ester	silastic	287.29	4.87	9.11	2	0	0.0675	-1.17	aq. saturated sol.	not available	N/A	static	phosphate buffered saline PH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
34	hexyl ester	silastic	301.29	5.36	9.07	2	0	0.107	-0.91	aq. saturated sol.	not available	N/A	static	phosphate buffered saline PH 7.4	37	24	UV-spectroscopy	*J.Pharm.Pharmacology*, 58: 167-177
35	pentachlorophenol	silastic	266.33	5.12	10.78	1	1	0.014	-1.85	ethanol	0.25 mm	N/A	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007
36	pentachlorophenol	silastic	266.33	5.12	10.78	1	1	0.029	-1.54	water	0.25 mm	N/A	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007
37	pentachlorophenol	silastic	266.33	5.12	10.78	1	1	0.01	-2	40% ethanol, 60% water	0.25 mm	N/A	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007
38	pentachlorophenol	silastic	266.33	5.12	10.78	1	1	0.012	-1.92	40% ethanol, 60% water, MNA	0.25 mm	N/A	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007
39	pentachlorophenol	silastic	266.33	5.12	10.78	1	1	0.005	-2.30	40% ethanol, 60% water, SLS	0.25 mm	N/A	flow-through	Krebs Ringer bicarbonate buffer & dextrose & BSA (4.5%)	37	8	radiolabelled (14C)	*Tox.Sciences*, 69: 295-305, 2007

Appendix 10. Species effect

Name	Species	MW	SP $(cal/cm^3)^{1/2}$	logP KOWWIN	Ha	Hd	log K_p (cmh^{-1})
1,6-hexanediol diglycidyl ether (HDDGE)	human	230.20	9.36	0.84	4	0	-3.87
1,6-hexanediol diglycidyl ether (HDDGE)	rodent	230.20	9.36	0.84	4	0	-3.40
2-(2-methoxyethoxy)ethanol	human	120.15	10.25	-1.18	3	1	-3.69
2-(2-methoxyethoxy)ethanol	rodent	120.15	10.25	-1.18	3	1	-1.10
2,4 dimethylamine	human	266.13	9.52	0.84	3	2	-3.02
2,4 dimethylamine	rodent	266.13	9.52	0.84	3	2	-3.51
2-ethoxyethanol	human	90.12	10.33	-0.42	2	1	-3.07
2-ethoxyethanol	rodent	90.12	10.33	-0.42	2	1	-3.83
2-phenoxyethanol	human	138.17	11.49	1.10	2	1	-2.87
2-phenoxyethanol	rodent	138.17	11.49	1.10	2	1	-2.75
2-phenylphenol	human	170.21	12.24	3.28	1	1	-1.74
2-phenylphenol	rodent	170.21	12.24	3.28	1	1	-1.58
4-n-butylaniline	human	149.24	9.51	3.10	1	1	-0.39
4-n-butylaniline	rodent	149.36	9.51	3.10	1	1	-0.64
4-n-pentylaniline	human	163.30	9.79	3.59	1	1	-0.65
4-n-pentylaniline	rodent	163.30	9.79	3.59	1	1	-0.61
5-fluorouracil	human	130.01	13.46	-0.81	3	2	-4.78
5-fluorouracil	rodent	130.01	13.46	-0.81	3	2	-4.22
aniline	human	93.10	10.83	1.08	1	1	-1.21
aniline	rodent	93.10	10.83	1.08	1	1	-1.17
atenolol	human	266.30	12.49	-0.03	4	3	-4.30
atenolol	rodent	266.30	12.49	-0.03	4	3	-1.52
benzoic acid	human	122.10	11.94	1.87	1	1	-2.88
benzoic acid	rodent	122.10	11.94	1.87	1	1	-2.02
bisphenol A diglycidyl ether (BADGE)	human	340.80	10.38	3.84	4	0	-6.32
bisphenol A diglycidyl ether (BADGE)	rodent	340.80	10.38	3.84	4	0	-5.26
butyl paraben	human	194.23	11.45	3.47	2	1	-1.25
caffeine	human	194.20	32.83	0.16	4	0	-3.68
caffeine	rodent	194.20	32.83	0.16	4	0	-2.99
clotrimazole	human	344.85	11.17	6.26	2	0	-2.70
clotrimazole	rodent	344.85	11.17	6.26	2	0	-2.26
corticosterone	human	346.50	11.91	1.99	4	2	-4.22
corticosterone	rodent	346.50	11.91	1.99	4	2	-3.28
cortisone	human	360.50	12.10	1.81	5	2	-5.00
cortisone	rodent	360.50	12.10	1.81	5	2	-3.33
coumarin	human	146.15	11.91	1.51	1	0	-2.04
coumarin	rodent	146.15	11.91	1.51	1	0	-3.00
DDT	human	354.49	9.45	6.79	0	0	-2.23
DDT	rodent	354.49	9.45	6.79	0	0	-2.17
DEHP	human	390.57	9.39	8.39	2	0	-5.24
DEHP	rodent	390.57	9.39	8.39	2	0	-3.02
DEP	human	222.24	10.51	2.65	2	0	-4.94
DEP	rodent	222.24	10.51	2.65	2	0	-3.43
dibutyl squarate	human	226.27	10.58	2.45	4	0	-4.70
dibutyl squarate	rodent	226.27	10.58	2.45	4	0	-3.07

Name	Species	MW	SP $(cal/cm^3)^{1/2}$	logP KOWWIN	Ha	Hd	log K_p (cmh^{-1})
dibutylphthalate	human	278.35	10.86	5.11	2	0	-5.64
dibutylphthalate	rodent	278.35	10.86	5.11	2	0	-4.05
diethyl squarate	human	170.16	11.50	4.07	4	0	-3.92
diethyl squarate	rodent	170.16	11.50	4.07	4	0	-3.00
dodecyl glycidyl ether (C12GE)	human	242.20	8.41	5.01	2	0	-5.48
dodecyl glycidyl ether (C12GE)	rodent	242.20	8.41	5.01	2	0	-4.54
epikote YX4000	human	354.40	11.00	5.19	4	0	-7.33
epikote YX4000	rodent	354.40	11.00	5.19	4	0	-1.01
ethanol	human	46.07	10.92	-0.14	1	1	-3.50
ethanol	rodent	46.07	10.92	-0.14	1	1	-3.38
ethylaniline	human	121.20	9.73	2.11	1	1	-0.54
ethylaniline	rodent	121.20	9.73	2.11	1	1	-0.94
etorphine	human	411.55	11.76	3.02	5	2	-2.44
etorphine	rodent	411.55	11.76	3.02	5	2	-2.34
hydrocortisone	human	362.50	12.75	1.62	5	3	-3.80
hydrocortisone	rodent	362.50	12.75	1.62	5	3	-4.00
hydroquinone	human	110.11	15.18	1.03	2	2	-5.03
hydroquinone	rodent	110.11	15.18	1.03	2	2	-4.66
ketoprofen	human	254.29	11.75	3.12	2	1	-3.21
ketoprofen	rodent	254.29	11.75	3.12	2	1	-1.73
lidocaine	human	234.34	8.78	1.66	2	1	-1.97
lidocaine	rodent	234.34	8.78	1.66	2	1	-2.05
linoleic acid	human	289.45	9.05	7.51	1	1	-4.97
linoleic acid	rodent	289.45	9.05	7.51	1	1	-4.54
mannitol	human	182.17	18.63	-3.01	6	6	-4.60
mannitol	rodent	182.17	18.53	-3.01	6	6	-3.64
methanol	human	32.04	11.68	-0.63	1	1	-2.80
methanol	rodent	32.04	11.68	-0.63	1	1	-2.74
methyl paraben	human	152.15	12.50	2.00	2	1	-1.67
methyl paraben	human	152.15	12.50	2.00	2	1	-5.23
morphine	human	285.30	13.68	0.72	4	2	-5.03
morphine	rodent	285.30	13.68	0.72	4	2	-3.82
nicorandil	human	211.18	14.40	0.43	3	1	-4.30
nicorandil	rodent	211.18	14.40	0.43	3	1	-3.00
N-N-diethyl m-toluamide	human	191.28	10.70	2.26	1	0	-2.65
N-N-diethyl m-toluamide	rodent	191.28	10.70	2.26	1	0	-2.77
n-octanol	human	130.23	9.45	2.81	1	1	-1.21
n-octanol	rodent	130.23	9.45	2.81	1	1	-1.01
nonane	human	128.30	7.51	4.76	0	0	-4.38
nonane	rodent	128.30	7.51	4.76	0	0	-4.38
o-cresyl glycidyl ether (oCGE)	human	164.20	10.38	2.16	2	0	-4.03
o-cresyl glycidyl ether (oCGE)	rodent	164.20	10.38	2.16	2	0	-3.87
paraquat	human	257.16	10.45	-2.71	0	0	-5.06
paraquat	rodent	257.16	10.45	-2.71	0	0	-3.46
progesterone	human	314.50	10.05	3.67	2	0	-1.52
progesterone	rodent	314.50	10.05	3.67	2	0	-1.96
propoxur	human	209.25	10.31	1.90	2	1	-3.05

Name	Species	MW	SP $(cal/cm^3)^{1/2}$	logP KOWWIN	Ha	Hd	log K_p (cmh^{-1})
propoxur	rodent	209.25	10.31	1.90	2	1	-2.43
salicylic acid	human	138.10	14.39	2.24	2	2	-1.89
salicylic acid	rodent	138.10	14.39	2.24	2	2	-1.98
squaric acid	human	114.06	20.47	-0.44	4	2	-5.12
squaric acid	rodent	114.06	20.47	-0.44	4	2	-3.15
terbinafine	human	291.40	9.33	5.81	1	0	-3.00
terbinafine	rodent	291.40	9.33	5.81	1	0	-1.26
testosterone	human	288.40	10.66	3.27	2	1	-2.17
testosterone	rodent	288.40	10.66	3.27	2	1	-2.74
theophylline	human	180.17	14.05	-0.39	4	1	-3.36
theophylline	rodent	180.17	14.05	-0.39	4	1	-2.66
triclosan	human	289.55	10.02	2.47	2	1	-4.47
triclosan	rodent	289.55	10.02	2.47	2	1	0.13
urea	rodent	60.60	14.36	-1.56	1	2	-3.15
urea	rodent	60.60	14.36	-1.56	1	2	-4.80
water	human	18.02	26.68	-1.38	1	1	-3.15
water	rodent	18.02	26.68	-1.38	1	1	-2.70

Appendix 11. Database B. Human skin dataset – Experimental vs predicted K_p values

Experimental permeability coefficients and drug properties

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	K_p (cmh^{-1})	Log K_p (cmh^{-1})
1	salicyclic acid	138.10	2.26 –a	13.13	0.006264	-2.20 –a
2	isoquinoline	129.20	2.03 –a	11.53	0.016812	-1.77 –a
3	amylobarbital	226.30	1.96 –a	12.27	0.002268	-2.64 –a
4	butabarbital	212.20	1.89 –a	13.13	0.000194	-3.71 –a
5	phenobarbital	232.20	1.47 –a	14.42	1.645200	0.22 –a
6	barbital	184.20	0.65 –a	14.20	0.000112	-3.95 –a
7	progesterone	314.50	3.70 –a	9.85	0.001512	-2.82 –a
8	pregnenolone	316.50	3.13 –a	10.91	0.001512	-2.82 –a
9	hydroxyprogesterone	332.50	2.47 –a	10.91	0.000598	-3.22 –a
10	hydroxypregnenolone	330.50	3.00 –a	10.91	0.000598	-3.22 –a
11	deoxycorticosterone	330.50	2.88 –a	18.37	0.000450	-3.35 –a
12	testosterone	288.40	3.31 –a	10.87	0.000396	-3.40 –a
13	cortexolone	346.50	2.52 –a	18.37	0.000076	-4.12 –a
14	corticosterone	346.50	1.94 –a	18.37	0.000061	-4.21 –a
15	cortisone	360.50	1.42 –a	18.37	0.000011	-4.97 –a
16	estrone	270.40	2.76 –a	14.51	0.003600	-2.44 –a
17	estradiol	272.40	2.69 –a	12.01	0.000288	-3.54 –a
18	estriol	288.40	2.47 –a	20.04	0.000040	-4.40 –a
19	methanol	32.00	4.77 –a	13.77	0.001008	-3.00 –a
20	ethanol	46.00	-0.31 –a	12.58	0.001008	-3.00 –a
21	propan-1-ol	60.00	0.25 –a	11.84	0.001404	-2.85 –a
22	butan-1-ol	74.00	0.88 –a	11.33	0.002484	-2.64 –a
23	pentan-1-ol	88.00	1.56 –a	10.96	0.005976	-2.22 –a
24	hexan-1-ol	102.20	2.03 –a	10.68	0.013068	-1.88 –a
25	heptan-1-ol	116.20	2.72 –a	10.46	0.032040	-1.49 –a
26	octan-1-ol	130.20	2.97 –a	10.28	0.052200	-1.28 –a
27	oxprenolol	265.40	2.62 –b	11.03	0.001549	-2.81 –b
28	metoprolol	267.40	2.28 –b	10.93	0.000832	-3.08 –b
29	atenolol	266.30	1.95 –b	13.24	0.061660	-1.21 –b
30	griseofulvin	352.80	2.07 –d	10.44	0.001288	-2.89 –d
31	griseofulvin	352.80	2.07 –d	10.44	0.001950	-2.71 –d
32	propranolol	295.84	0.56 –b	11.96	0.070795	-1.15 –b
33	idomethacin	357.80	3.08 –e	12.35	0.000009	-5.39 –e
34	ibuprofen	206.30	3.51 –e	10.00	0.036308	-1.44 –e
35	morphine	285.30	0.62 –c	13.10	0.000009	-5.03 –c
36	hydromorphine	285.30	1.25 –c	11.70	0.000015	-4.82 –c
37	codeine	299.30	0.89 –c	10.90	0.000049	-4.31 –c
38	fentanyl	336.50	4.37-c	9.80	0.010000	-2.00 –c
39	sufentanyl	387.50	4.59 –c	9.70	0.012023	-1.92 –c
40	meperidine	247.00	2.72 –c	9.60	0.003715	-2.43 –c
41	dexamethasone	392.47	1.83 – k	11.98	0.000065	-4.19 – k
42	corticosterone	346.45	3.32 – i	18.37	0.000891	-3.05 – i
43	atenolol	266.00	1.77 – j	13.24	0.000145	-3.84 – j
44	hydrocortisone 21 - (N/N -dime) succ	489.61	2.03 –a	12.22	0.000068	-4.17 –a
45	hydrocortisone 21 propionate	418.50	3.00 –a	12.33	0.003388	-2.47 –a

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	K_p (cmh^{-1})	Log K_p (cmh^{-1})
46	hydrocortisone 21 - pimelamate	503.63	2.31 –a	14.23	0.000891	-3.05 –a
47	hydrocortisone 21 - octanoate	488.66	5.49 –a	10.55	0.061660	-1.21 –a
48	hydrocortisone 21 - methylsuccinate	476.57	2.58 –a	12.44	0.000209	-3.68 –a
49	hydrocortisone 21 - methylpimelate	518.65	3.70 –a	11.39	0.005370	-2.27 –a
50	hydrocortisone 21 - hexanoate	460.61	4.48 –a	11.01	0.017783	-1.75 –a
51	hydrocortisone 21 - hemisuccinate	462.54	2.11 –a	14.48	0.000631	-3.20 –a
52	hydrocortisone 21 - hemipimelate	504.62	2.31 –a	12.68	0.002778	-2.75 –a
53	hydrocortisone 21 (6-OH) hexanoate	476.61	2.79 –a	13.82	0.000912	-3.04 –a
54	hydrocortisone 21 - succinamate	461.60	1.43 –a	16.90	0.000026	-4.59 –a
55	bufexamac	223.30	2.43 –f	13.33	0.004169	-2.38 –f
56	diclofenac sodium	318.10	4.40 –f	12.76	0.000355	-3.45 –f
57	felbinac	212.20	3.26 –f	11.86	0.019055	-1.72 –f
58	furbiprofen	244.30	4.12 –f	11.62	0.048978	-1.31 –f
59	naproxen	230.30	3.00 –f	11.47	0.002884	-2.54 –f
60	aspirin	180.16	1.02 –g	12.21	0.007244	-2.14 –h
61	benzoic acid	122.10	1.88 – h	11.52	0.025119	-1.60 – h
62	sucrose	342.30	-2.25 – i	16.07	0.000005	-5.28- i
63	b-estradiol	272.37	2.69 – i	12.01	0.005248	-2.28 – i
64	phenol	94.11	1.46 – i	13.46	0.008128	-2.09 – i
65	raffinose	504.00	-4.30 – j	18.73	0.000083	-4.08 – j
66	mannitol	182.00	-3.10 – j	18.53	0.001122	-2.95 – j
67	salicyclic acid	138.00	-2.14 – j	13.13	0.000646	-3.19 – j
68	pindolol	248.00	-0.33 – j	12.10	0.000282	-3.55 – j
69	aprenolol	249.00	0.65 – j	10.86	0.002291	-2.64 – j
70	aldosterone	360.04	1.08 – j	18.37	0.000159	-3.80 – j

References
a - from Ghafourian & Fooladi (2001)
b - from Modamio et al. (2000)
c - from Roy & Flynn (1989)
d - from Ritschel et al. (1989)
e - from Hadgraft et al. (2000a)
f - from *The Pharmaceutical Codex*
g - from Fang et al. (2003)
h - from Degim et al. (1998)
i - from the Flynn dataset (1990)
j - from Suhonen et al. (2003)
k - from Johnson et al. (1997)

Predicted permeability coefficient(s) using different models

1. Human skin – Predicted skin permeability using the Potts and Guy (1992) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Potts & Guy) (cmh^{-1})	Log K_p (exp) - log K_p (Potts & Guy) (cmh^{-1})
1	salicyclic acid	-2.20	-1.94	-0.27
2	isoquinoline	-1.77	-2.05	0.27
3	amylobarbital	-2.64	-2.69	0.04
4	butabarbital	-3.71	-2.65	-1.06
5	barbital	-3.95	-3.36	-0.59

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Potts & Guy) (cmh^{-1})	Log K_p (exp) - log K_p (Potts & Guy) (cmh^{-1})
6	progesterone	-2.82	-1.99	-0.83
7	pregnenolone	-2.82	-2.41	-0.41
8	hydroxyprogesterone	-3.22	-2.97	-0.25
9	hydroxypregnenolone	-3.22	-2.59	-0.64
10	deoxycorticosterone	-3.35	-2.67	-0.68
11	testosterone	-3.40	-2.11	-1.29
12	cortexolone	-4.12	-3.02	-1.10
13	corticosterone	-4.21	-3.44	-0.78
14	cortisone	-4.97	-3.89	-1.08
15	estrone	-2.44	-2.39	-0.05
16	estradiol	-3.54	-2.45	-1.10
17	estriol	-4.40	-2.71	-1.70
18	ethanol	-2.00	-3.20	0.20
19	propan-1-ol	-2.85	-2.89	0.04
20	butan-1-ol	-2.60	-2.53	-0.08
21	pentan-1-ol	-2.22	-2.13	-0.09
22	hexan-1-ol	-1.88	-1.88	-0.00
23	heptan-1-ol	-1.49	-1.48	-0.02
24	octan-1-ol	-1.28	-1.39	0.10
25	oxprenolol	-2.81	-2.46	-0.35
26	metoprolol	-3.08	-2.71	-0.37
27	atenolol	-1.21	-2.94	1.73
28	griseofulvin	-2.89	-3.38	0.49
29	griseofulvin	-2.71	-3.38	0.67
30	propranolol	-1.15	-4.11	2.96
31	indomethacin	-5.39	-2.70	-2.69
32	ibuprofen	-1.44	-1.47	0.03
33	morphine	-5.03	-4.00	-1.03
34	hydromorphine	-4.82	-3.55	-1.27
35	codeine	-4.31	-3.89	-0.42
36	fentanyl	-2.00	-1.65	-0.35
37	sufentanyl	-1.92	-1.80	-0.12
38	meperidine	-2.43	-2.28	-0.15
39	dexamethasone	-4.19	-3.79	-0.40
40	corticosterone	-3.05	-2.46	-0.59
41	atenolol	-3.84	-3.07	-0.77
42	hydrocortisone 21 - (N/N -dime) succ	-4.17	-4.25	0.08
43	hydrocortisone 21 proprionate	-2.47	-3.12	0.65
44	hydrocortisone 21 - octanoate	-1.21	-1.78	0.57
45	hydrocortisone 21 - methylsuccinate	-3.68	-3.78	0.10
46	hydrocortisone 21 - hexanoate	-1.75	-2.33	0.58
47	hydrocortisone 21 - hemisuccinate	-3.20	-4.02	0.82
48	hydrocortisone 21 (6-OH) hexanoate	-3.04	-3.63	0.59
49	hydrocortisone 21 - succinamate	-4.59	-4.50	-0.09
50	bufexamac	-2.38	-2.34	-0.04
51	diclofenac sodium	-3.45	-1.52	-1.93

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Potts & Guy) (cmh^{-1})	Log K_p (exp) - log K_p (Potts & Guy) (cmh^{-1})
52	felbinac	-1.72	-1.68	-0.04
53	flurbiprofen	-1.31	-1.27	-0.04
54	naproxen	-2.54	-1.97	-0.57
55	aspirin	-2.14	-3.07	0.93
56	benzoic acid	-1.60	-2.11	0.51
57	sucrose	-5.28	-6.39	1.11
58	b-estradiol	-2.28	-2.45	0.17
59	phenol	-2.09	-2.24	0.15
60	salicyclic acid	-3.19	-5.06	1.87
61	pindolol	-3.55	-4.45	0.90
62	alprenolol	-2.64	-3.76	1.12
63	aldosterone	-3.80	-4.13	0.33

The following compounds were eliminated from the human skin dataset due to high molecular weights and/or unfavourable log P values. Phenobarbital and methanol were eliminated as different literature sources gave largely variable log P values.

No	Name	MW	Log P KOWWIN	Log K_p (exp) (cmh^{-1})	Log K_p (Potts & Guy) (cmh^{-1})	Log K_p (exp)- log K_p (Potts & Guy) (cmh^{-1})
1	phenobarbital	232.20	1.47	0.22	-3.07	3.29
2	methanol	32.00	4.77	-3.00	0.49	-3.49
3	hydrocortisone 21 - pimelamate	503.63	2.31	-3.05	-4.13	1.08
4	hydrocortisone 21 - methylpimelate	518.65	3.70	-2.27	-3.24	0.97
5	hydrocortisone 21 - hemipimelate	504.62	2.31	-2.75	-4.14	1.40
6	raffinose	504.00	-4.30	-4.08	-8.83	4.75
7	mannitol	182.00	-3.10	-2.95	-6.01	3.06

2. Human skin – Predicted skin permeability using the revised Robinson (1995) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Robinson) (cmh^{-1})	Log K_p (exp)- log K_p (Robinson) (cmh^{-1})
1	salicyclic acid	-2.20	-2.06	-0.14
2	isoquinoline	-1.77	-2.13	0.36
3	amylobarbital	-2.64	-2.82	0.18
4	butabarbital	-3.71	-2.77	-0.94
5	barbital	-3.95	-3.35	-0.61
6	progesterone	-2.82	-2.25	-0.57
7	pregnenolone	-2.82	-2.61	-0.21
8	hydroxyprogesterone	-3.22	-3.07	-0.15
9	hydroxypregnenolone	-3.22	-2.75	-0.48
10	deoxycorticosterone	-3.35	-2.83	-0.52
11	testosterone	-3.40	-2.35	-\1.05
12	cortexolone	-4.12	-3.11	-1.01
13	corticosterone	-4.21	-3.46	-0.75
14	cortisone	-4.97	-3.83	-1.14
15	estrone	-2.44	-2.59	0.14
16	estradiol	-3.54	-2.64	-0.90
17	estriol	-4.40	-2.86	-1.55

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Robinson) (cmh^{-1})	Log K_p (exp)- log K_p (Robinson) (cmh^{-1})
18	ethanol	-3.00	-2.74	-0.26
19	propan-1-ol	-2.85	-2.55	-0.30
20	butan-1-ol	-2.60	-2.33	-0.27
21	pentan-1-ol	-2.22	-2.06	-0.16
22	hexan-1-ol	-1.88	-1.91	0.03
23	heptan-1-ol	-1.49	-1.64	0.14
24	octan-1-ol	-1.28	-1.60	0.32
25	oxprenolol	-2.81	-2.64	-0.17
26	metoprolol	-3.08	-2.85	-0.23
27	atenolol	-1.21	-3.09	1.88
28	griseofulvin	-2.89	-3.39	0.50
29	griseofulvin	-2.71	-3.39	0.68
30	propranolol	-1.15	-4.05	2.90
31	indomethacin	-5.39	-2.83	-2.56
32	ibuprofen	-1.44	-1.79	0.35
33	morphine	-5.03	-3.92	-1.11
34	hydromorphine	-4.82	-3.57	-1.25
35	codeine	-4.31	-3.86	-0.45
36	fentanyl	-2.00	-1.97	-0.03
37	sufentanyl	-1.92	-2.07	0.15
38	meperidine	-2.43	-2.48	0.05
39	dexamethasone	-4.19	-3.73	-0.46
40	corticosterone	-3.05	-2.63	-0.42
41	atenolol	-3.84	-3.16	-0.68
42	hydrocortisone 21 - (N/N -dime) succ	-4.17	-4.01	-0.16
43	hydrocortisone 21 proprionate	-2.47	-3.15	0.68
44	hydrocortisone 21 - octanoate	-1.21	-1.97	0.76
45	hydrocortisone 21 - methylsuccinate	-3.68	-3.64	-0.04
46	hydrocortisone 21 - hexanoate	-1.75	-2.44	0.69
47	hydrocortisone 21 - hemisuccinate	-3.20	-3.86	0.66
48	hydrocortisone 21 (6-OH) hexanoate	-3.04	-3.51	0.47
49	hydrocortisone 21 - succinamate	-4.59	-4.24	-0.35
50	bufexamac	-2.38	-2.52	0.14
51	diclofenac sodium	-3.45	-1.87	-1.58
52	felbinac	-1.72	-1.97	0.25
53	furbiprofen	-1.31	-1.67	0.36
54	naproxen	-2.54	-2.22	-0.32
55	aspirin	-2.14	-3.10	0.96
56	benzoic acid	-1.60	-2.17	0.57
57	sucrose	-5.28	-5.04	-0.24
58	b-estradiol	-2.28	-2.64	0.36
59	phenol	-2.09	-2.18	0.09
60	salicyclic acid	-3.19	-4.50	1.31
61	pindolol	-3.55	-4.25	0.70
62	alprenolol	-2.64	-3.72	1.08
63	aldosterone	-3.80	-4.02	0.22

The following compounds were excluded from the human skin dataset.

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Robinson) (cmh^{-1})	Log K_p (exp)- log K_p (Robinson) (cmh^{-1})
1	phenobarbital	0.22	-3.14	3.36
2	methanol	-3.00	-0.40	-2.59
3	hydrocortisone 21 - pimelamate	-3.05	-3.90	0.85
4	hydrocortisone 21 – methylpimelate	-2.27	-3.14	0.87
5	hydrocortisone 21 – hemipimelate	-2.75	-3.90	1.15
6	raffinose	-4.08	-5.17	1.09
7	mannitol	-2.95	-4.86	1.91

3. Human skin – Predicted skin permeability using the Cronin et al. (1999) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp) - log K_p (Cronin) (cmh^{-1})
1	salicyclic acid	-2.20	-2.01	-0.19
2	isoquinoline	-1.77	-2.10	0.32
3	amylobarbital	-2.64	-3.15	0.51
4	butabarbital	-3.71	-3.06	-0.65
5	barbital	-3.95	-3.73	-0.23
6	progesterone	-2.82	-2.72	-0.10
7	pregnenolone	-2.82	-3.18	0.36
8	hydroxyprogesterone	-3.22	-3.85	0.63
9	hydroxypregnenolone	-3.22	-3.42	0.20
10	deoxycorticosterone	-3.35	-3.52	0.17
11	testosterone	-3.40	-2.75	-0.65
12	cortexolone	-4.12	-3.96	-0.16
13	corticosterone	-4.21	-4.40	0.19
14	cortisone	-4.97	-4.95	-0.02
15	estrone	-2.44	-2.99	0.55
16	estradiol	-3.54	-3.06	-0.48
17	estriol	-4.40	-3.40	-1.00
18	ethanol	-3.00	-3.04	0.05
19	propan-1-ol	-2.85	-2.76	-0.10
20	butan-1-ol	-2.60	-2.41	-0.19
21	pentan-1-ol	-2.22	-2.04	-0.19
22	hexan-1-ol	-1.88	-1.82	-0.06
23	heptan-1-ol	-1.49	-1.43	-0.06
24	octan-1-ol	-1.28	-1.38	0.10
25	oxprenolol	-2.81	-3.05	0.24
26	metoprolol	-3.08	-3.33	0.25
27	atenolol	-1.21	-3.57	2.36
28	griseofulvin	-2.89	-4.37	1.48
29	griseofulvin	-2.71	-4.37	1.66
30	propranolol	-1.15	-4.95	3.80
31	indomethacin	-5.39	-3.64	-1.75
32	ibuprofen	-1.44	-1.75	0.31
33	morphine	-5.03	-4.79	-0.24
34	hydromorphine	-4.82	-4.31	-0.51
35	codeine	-4.31	-4.73	0.42
36	fentanyl	-2.00	-2.43	0.43
37	sufentanyl	-1.92	-2.79	0.87
38	meperidine	-2.43	-2.78	0.35
39	dexamethasone	-4.19	-4.96	0.77
40	corticosterone	-3.05	-3.34	0.29
41	atenolol	-3.84	-3.71	-0.13
42	hydrocortisone 21 - (N/N -dime) succ	-4.17	-5.81	1.64
43	hydrocortisone 21 proprionate	-2.47	-4.33	1.86
44	hydrocortisone 21 - octanoate	-1.21	-3.14	1.93
45	hydrocortisone 21 - methylsuccinate	-3.68	-5.25	1.57

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp) - log K_p (Cronin) (cmh^{-1})
46	hydrocortisone 21 - hexanoate	-1.75	-3.63	1.87
47	hydrocortisone 21 - hemisuccinate	-3.20	-5.47	2.27
48	hydrocortisone 21 (6-OH) hexanoate	-3.04	-5.09	2.05
49	hydrocortisone 21 - succinamate	-4.59	-5.98	1.39
50	bufexamac	-2.38	-2.76	0.38
51	diclofenac sodium	-3.45	-2.22	-1.23
52	felbinac	-1.72	-2.01	0.29
53	flurbiprofen	-1.31	-1.67	0.36
54	naproxen	-2.54	-2.39	-0.15
55	aspirin	-2.14	-3.40	1.26
56	benzoic acid	-1.60	-2.14	0.54
57	sucrose	-5.28	-7.59	2.31
58	b-estradiol	-2.28	-3.06	0.78
59	phenol	-2.09	-2.18	0.09
60	salicyclic acid	-3.19	-5.40	2.21
61	pindolol	-3.55	-5.14	1.59
62	alprenolol	-2.64	-4.39	1.75
63	aldosterone	-3.80	-5.21	1.41

The following compounds were excluded from the human skin dataset.

No	Name	MW	Log P KOWWIN	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp) – log K_p (Cronin) (cmh^{-1})
1	phenobarbital	232.20	1.47	0.22	-3.60	3.81
2	methanol	32.00	4.77	-3.00	1.01	-4.01
3	hydrocortisone 21 - pimelamate	503.63	2.31	-3.05	-5.74	2.69
4	hydrocortisone 21 - hemipimelate	504.62	2.31	-2.75	-5.75	3.00
5	hydrocortisone 21 - methylpimelate	518.65	3.70	-2.27	-4.82	2.55
6	raffinose	504.00	-4.30	-4.08	-10.83	6.75
7	mannitol	182.00	-3.10	-2.95	-6.59	3.64

4. Human skin – Predicted skin permeability using the revised Brown and Rossi (1995) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp) - log K_p (Brown & Rossi) (cmh^{-1})
1	salicyclic acid	-2.20	-1.53	-0.67
2	isoquinoline	-1.77	-1.66	-0.11
3	amylobarbital	-2.64	-1.70	-0.94
4	butabarbital	-3.71	-1.75	-1.96
5	barbital	-3.95	-2.60	-1.35
6	progesterone	-2.82	-1.08	-1.74
7	pregnenolone	-2.82	-1.19	-1.63
8	hydroxyprogesterone	-3.22	-1.43	-1.79
9	hydroxypregnenolone	-3.22	-1.22	-2.00
10	deoxycorticosterone	-3.35	-1.26	-2.08
11	testosterone	-3.40	-1.14	-2.26
12	cortexolone	-4.12	-1.41	-2.72
13	corticosterone	-4.21	-1.72	-2.50
14	cortisone	-4.97	-2.05	-2.91
15	estrone	-2.44	-1.31	-1.14
16	estradiol	-3.54	-1.33	-2.21
17	estriol	-4.40	-1.43	-2.97

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp) - log K_p (Brown & Rossi) (cmh^{-1})
18	ethanol	-3.00	-3.31	0.32
19	propan-1-ol	-2.85	-2.90	0.04
20	butan-1-ol	-2.60	-2.44	-0.17
21	pentan-1-ol	-2.22	-1.96	-0.26
22	hexan-1-ol	-1.88	-1.66	-0.22
23	heptan-1-ol	-1.49	-1.32	-0.17
24	octan-1-ol	-1.28	-1.23	-0.05
25	oxprenolol	-2.81	-1.36	-1.45
26	metoprolol	-3.08	-1.52	-1.56
27	atenolol	-1.21	-1.71	0.50
28	griseofulvin	-2.89	-1.64	-1.25
29	griseofulvin	-2.71	-1.64	-1.07
30	propranolol	-1.15	-2.67	1.52
31	indomethacin	-5.39	-1.20	-4.19
32	ibuprofen	-1.44	-1.11	-0.33
33	morphine	-5.03	-2.62	-2.41
34	hydromorphine	-4.82	-2.17	-2.65
35	codeine	-4.31	-2.43	-1.88
36	fentanyl	-2.00	-1.03	-0.97
37	sufentanyl	-1.92	-1.02	-0.90
38	meperidine	-2.43	-1.32	-1.11
39	dexamethasone	-4.19	-1.78	-2.41
40	corticosterone	-3.05	-1.14	-1.91
41	atenolol	-3.84	-1.82	-2.02
42	hydrocortisone 21 - (N/N -dime) succ	-4.17	-1.66	-2.51
43	hydrocortisone 21 proprionate	-2.47	-1.22	-1.25
44	hydrocortisone 21 - pimelamate	-3.05	-1.51	-1.54
45	hydrocortisone 21 - octanoate	-1.21	-1.00	-0.21
46	hydrocortisone 21 - methylsuccinate	-3.68	-1.38	-2.30
47	hydrocortisone 21 - methylpimelate	-2.27	-1.08	-1.19
48	hydrocortisone 21 - hexanoate	-1.75	-1.02	-0.73
49	hydrocortisone 21 - hemisuccinate	-3.20	-1.62	-1.58
50	hydrocortisone 21 - hemipimelate	-2.75	-1.51	-1.24
51	hydrocortisone 21 (6-OH) hexanoate	-3.04	-1.29	-1.75
52	hydrocortisone 21 - succinamate	-4.59	-2.05	-2.54
53	bufexamac	-2.38	-1.45	-0.93
54	diclofenac sodium	-3.45	-1.03	-2.42
55	felbinac	-1.72	-1.16	-0.56
56	flurbiprofen	-1.31	-1.04	-0.27
57	naproxen	-2.54	-1.22	-1.32
58	aspirin	-2.14	-2.33	0.19
59	benzoic acid	-1.60	-1.75	0.15
60	sucrose	-5.28	-4.77	-0.51
61	b-estradiol	-2.28	-1.33	-0.95
62	phenol	-2.09	-2.03	-0.06
63	salicyclic acid	-3.19	-4.69	1.50

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp) - log K_p (Brown & Rossi) (cmh^{-1})
64	pindolol	-3.55	-3.33	-0.22
65	aprenolol	-2.64	-2.60	-0.04
66	aldosterone	-3.80	-2.29	-1.51

The following compounds were eliminated due to being outside the constraints set. The log P values for phenobarbital and methanol varied considerably according to different literature sources. Therefore, both were eliminated.

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp) – log K_p (Brown & Rossi) (cmh^{-1})
1	phenobarbital	0.22	-2.02	2.24
2	methanol	-3.00	-1.01	-1.98
3	raffinose	-4.08	-6.30	2.22
4	mannitol	-2.95	-5.40	2.45

Figure 1. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (pred) (cmh^{-1}) estimated by the Potts and Guy model.

$R^2 = 0.4029$

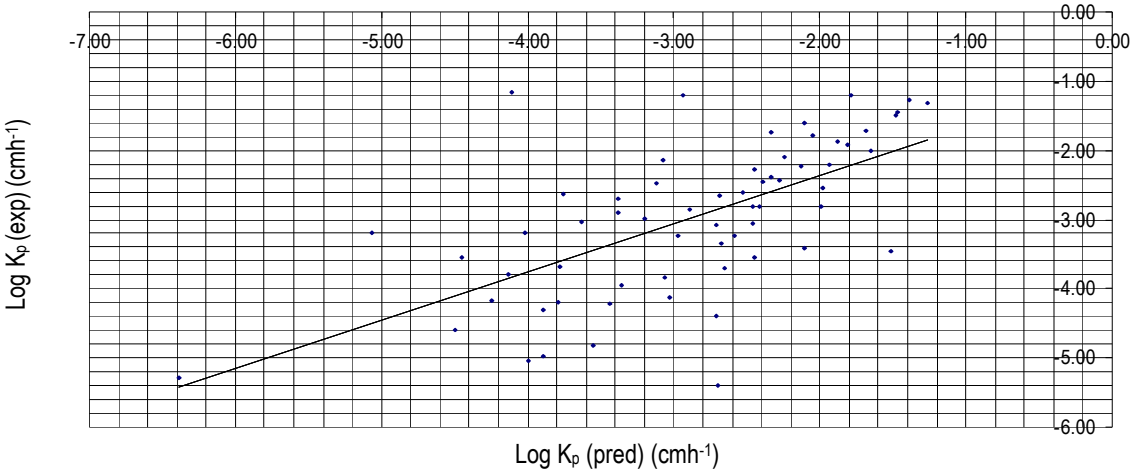


Figure 2. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (pred) (cmh^{-1}) estimated by the Cronin model.

$R^2 = 0.4214$

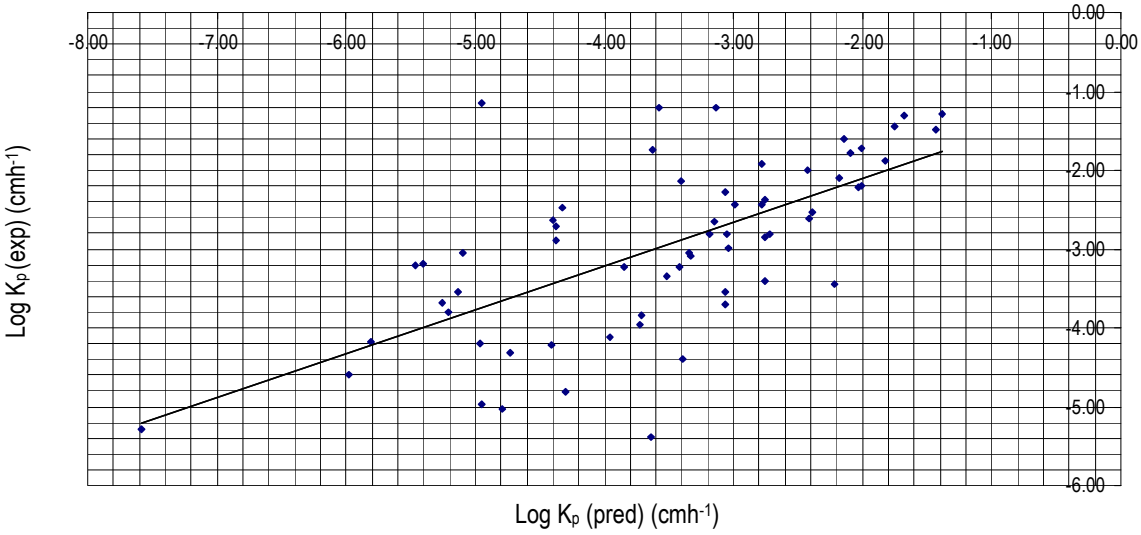


Figure 3. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (pred) (cmh^{-1}) estimated by the Robinson model.

$R^2 = 0.4269$

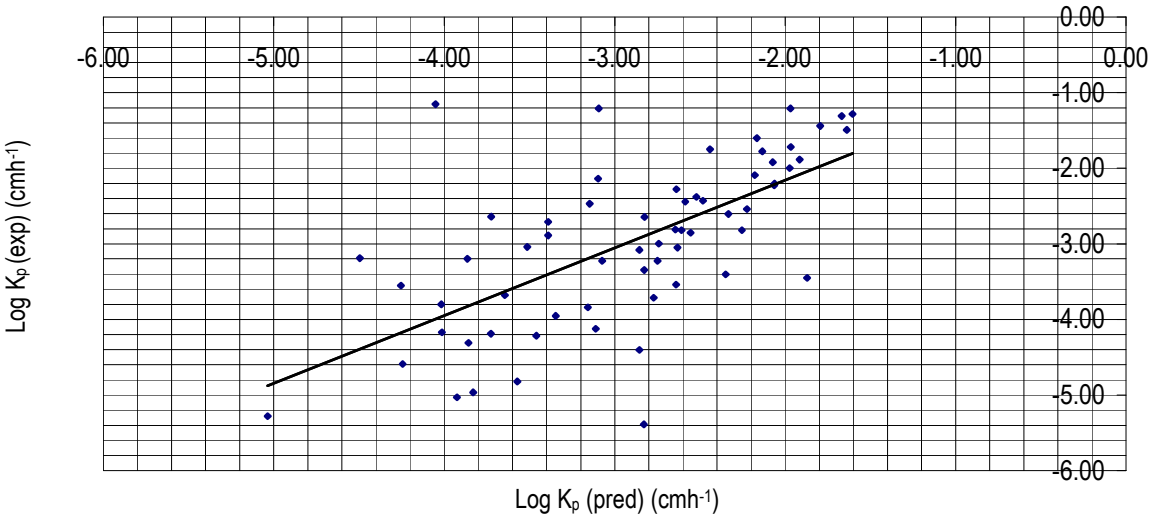
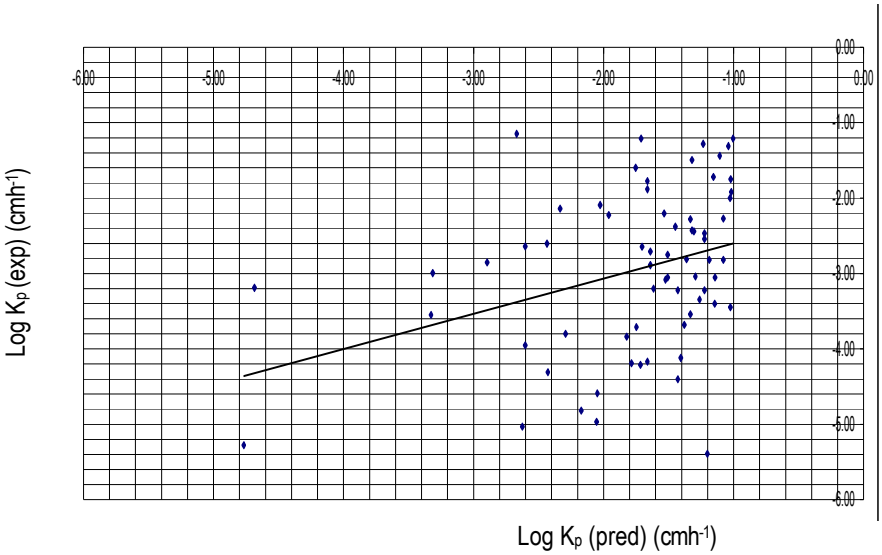


Figure 4. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (pred) (cmh^{-1}) estimated by the Brown and Rossi model.



Appendix 12. Database B. Mouse skin dataset – Experimental vs predicted K_p values

Mouse skin dataset - Experimental permeability coefficients and drug properties

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	K_p (cmh^{-1})	Log K_p (cmh^{-1})
1	theophylline	180.00	-0.25 – b	14.05	0.6600	-0.18 – a
2	5 fluorouracil	130.01	2.70 – b	14.99	4.3100	0.63 – a
3	bis (1-piperindyl) methyl 5FU	324.00	2.70 – b	11.04	0.0110	-1.96- a
4	1,3 bis (4-morpholinyl) methyl 5FU	328.00	2.70 – b	11.46	0.0430	-1.37 – a
5	7-(dibutylamino) methyl theophylline	321.00	-0.25 – b	10.98	0.0035	-2.46 – a
6	7-(piperindyl) methyl theophylline	277.00	-0.25 – b	12.04	0.0140	-1.85 – a
7	progesterone	314.50	3.70 – d	10.91	0.0756	-1.12 – c
8	estradiol	272.40	2.69 – d	12.01	0.0079	-2.10 – c
9	hydrocortisone	362.50	1.53 – e	12.38	0.0004	-3.44 – c
10	ethanol	46.00	-0.31 – f	12.58	0.0027	-2.57 – f
11	propanol	60.00	0.21 – f	11.84	0.0043	-2.37 – f
12	butanol	74.00	0.83 – f	11.33	0.0087	-2.06 – f
13	pentanol	88.00	1.37 – f	10.96	0.0163	-1.79 – f
14	hexanol	102.20	2.02 – f	10.68	0.0317	-1.50 – f
15	heptanol	116.20	2.40 –f	10.46	0.0704	-1.15 – f
16	octanol	130.20	2.97 – f	10.28	0.1289	-0.89 – f
17	methanol	32.00	-0.70 – f	13.77	0.0037	-2.43 – f
18	fentanyl	336.50	4.37 – h	9.80	0.0081	-2.09 – g
19	estradiol	272.40	2.69 – d	12.01	0.0159	-1.80 – g
20	mannitol	182.00	-3.10 – i	18.53	0.0009	-3.06 – g
21	corticosterone	346.50	1.94 – j	18.37	0.0008	-3.10 – j
22	corticosterone (PVP/PBS)	346.50	1.94 – j	18.37	0.0009	-3.06 – j
23	atenolol	266.34	-1.83 – k	13.24	0.2800	-0.55 – k
24	propranolol	295.30	0.56 – k	11.96	0.00005	-4.35 – k
25	propranolol HCL	295.84	0.56 - k	11.96	0.0750	-1.12 – k
26	oxprenolol	301.80	2.37 - k	11.03	0.0052	-2.28 – k
27	prednisolone heptanoate	472.62	4.08 – l	12.02	0.0001	-4.11 – l
28	prednisolone octanoate	486.65	4.39 – l	11.89	0.0001	-3.96 – l
29	prednisolone nonanoate	500.68	4.66 – l	11.78	0.0001	-4.04 – l
30	prednisolone decanoate	514.70	5.15 – l	11.67	0.0001	-3.95 – l
31	prednisolone undecanoate	528.73	5.54 – l	11.57	0.0002	-3.83 – l
32	prednisolone tridecanoate	556.78	6.02 – l	11.39	0.0001	-3.97 – l
33	prednisolone pentadecanoate	584.84	6.79 – l	11.23	0.0001	-4.00 – l
34	metoprolol	267.00	1.88 – k	10.93	0.0028	-2.56 – k
35	nifedipine	346.30	3.14 – m	11.23	0.0017	-2.77 – m
36	diclofenac sodium	318.10	1.13 – n	12.76	0.0003	-3.54 – n
37	hydrocortisone	362.50	1.53 – e	12.38	0.0001	-3.92 – e
38	hydrocortisone (DPY)	362.50	1.53 – e	12.38	0.0026	-2.59 – e
39	hydrocortisone (DPI)	362.50	1.53 – e	12.38	0.0025	-2.61 – e
40	hydrocortisone (DMEA)	362.50	1.53 – e	12.38	0.0016	-2.81 – e
41	hydrocortisone (DMEI)	362.50	1.53 – e	12.38	0.0006	-3.22 – e
42	hydrocortisone (DDE)	362.50	1.53 – e	12.38	0.0008	-3.08 – e
43	hydrocortisone (ND)	362.50	1.53 – e	12.38	0.0007	-3.13 – e

References

a - from Waranis & Sloan (1987)
b - from *The Pharmaceutical Codex*
c - from Knutson et al. (1993)
d - from Ghafourian & Fooladi (2001)
e - from Fuhrman et al. (1997)

f - from Shah et al. (1990)
g - from Liaw & Lin (2000)
h - from Roy & Flynn (1989)
i - from Suhonen et al. (2003)
j - from Shaker (2003)
k - from Ghosh et al. (1992)
l - from Hashiguchi et al. (1997)
m - from Diez et al. (1991)
n – from Arellano et al. (1996)
o – from Jain et al. (1995)

Predicted permeability coefficient(s) for mouse skin using different models

1. Mouse skin – Predicted skin permeability using the Potts and Guy (1992) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Potts & Guy) (cmh^{-1})	Log K_p (exp) – log K_p (Potts & Guy) (cmh^{-1})
1	theophylline	-0.18	-3.98	3.80
2	5 fluorouracil	0.63	-1.58	2.21
3	bis (1-piperindyl) methyl 5FU	-1.96	-2.76	0.80
4	1,3 bis (4-morpholinyl) methyl 5FU	-1.37	-2.78	1.42
5	7-(dibutylamino) methyl theophylline	-2.46	-4.84	2.38
6	7-(piperindyl) methyl theophylline	-1.85	-4.57	2.71
7	progesterone	-1.12	-1.99	0.87
8	estradiol	-2.10	-2.45	0.35
9	hydrocortisone	-3.44	-3.82	0.38
10	ethanol	-2.57	-3.20	0.63
11	propanol	-2.37	-2.92	0.55
12	butanol	-2.06	-2.56	0.50
13	pentanol	-1.79	-2.26	0.48
14	hexanol	-1.50	-1.89	0.39
15	heptanol	-1.15	-1.70	0.55
16	octanol	-0.89	-1.39	0.50
17	methanol	-2.43	-3.39	0.96
18	fentanyl	-2.09	-1.65	-0.44
19	estradiol	-1.80	-2.45	0.65
20	corticosterone	-3.10	-3.44	0.33
21	corticosterone (PVP/PBS)	-3.06	-3.44	0.37
22	atenolol	-0.55	-5.62	5.07
23	propranolol	-4.35	-4.10	-0.24
24	propranolol HCL	-1.12	-4.11	2.98
25	oxprenolol	-2.28	-2.86	0.58
26	prednisolone heptanoate	-4.11	-2.69	-1.43
27	prednisolone octanoate	-3.96	-2.55	-1.41
28	metoprolol	-2.56	-2.99	0.43
29	nifedipine	-2.77	-2.58	-0.19
30	diclofenac sodium	-3.54	-3.84	0.29
31	hydrocortisone	-3.92	-3.82	-0.10
32	hydrocortisone (azone)	-2.67	-3.82	1.16
33	hydrocortisone (DPY)	-2.59	-3.82	1.23
34	hydrocortisone (DPI)	-2.61	-3.82	1.22
35	hydrocortisone (DMEA)	-2.81	-3.82	1.02
36	hydrocortisone (DMEI)	-3.22	-3.82	0.60
37	hydrocortisone (DDE)	-3.08	-3.82	0.75
38	hydrocortisone (ND)	-3.13	-3.82	0.69
39	atenolol	-1.52	-5.62	4.10

The following compounds were eliminated because they have molecular weights greater than 500. Mannitol has a log P value of -3.10, and thus is eliminated because the value lies outside the constraints set.

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Potts & Guy) (cmh^{-1})	Log K_p (exp)- log K_p (Potts & Guy) (cmh^{-1})
1	prednisolone nonanoate	-4.04	-2.45	-1.59
2	prednisolone decanoate	-3.95	-2.18	-1.77
3	prednisolone undecanoate	-3.83	-1.99	-1.83
4	prednisolone tridecanoate	-3.97	-1.82	-2.15
5	prednisolone pentadecanoate	-4.01	-1.45	-2.56
6	mannitol	-3.06	-6.01	2.95

2. Mouse skin – Predicted skin permeability using the revised Brown and Rossi (1995) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp)- log K_p (Brown & Rossi) (cmh^{-1})
1	theophylline	-0.18	-3.27	3.09
2	5 fluorouracil	0.63	-1.33	1.96
3	bis (1-piperindyl) methyl 5FU	-1.96	-1.33	-0.63
4	1,3 bis (4-morpholinyl) methyl 5FU	-1.37	-1.33	-0.04
5	7-(dibutylamino) methyl theophylline	-2.46	-3.27	0.81
6	7-(piperindyl) methyl theophylline	-1.85	-3.27	1.42
7	progesterone	-1.12	-1.08	-0.04
8	estradiol	-2.10	-1.33	-0.77
9	hydrocortisone	-3.44	-1.98	-1.46
10	ethanol	-2.57	-3.31	0.75
11	propanol	-2.37	-2.93	0.56
12	butanol	-2.06	-2.47	0.41
13	pentanol	-1.79	-2.09	0.30
14	hexanol	-1.50	-1.67	0.17
15	heptanol	-1.15	-1.46	0.31
16	octanol	-0.89	-1.23	0.34
17	methanol	-2.43	-3.60	1.17
18	fentanyl	-2.09	-1.03	-1.07
19	estradiol	-1.80	-1.33	-0.47
20	corticosterone	-3.10	-1.72	-1.38
21	corticosterone (PVP/PBS)	-3.06	-1.72	-1.35
22	atenolol	-0.55	-5.20	4.64
23	propranolol	-4.35	-2.67	-1.68
24	propranolol HCL	-1.12	-2.67	1.54
25	oxprenolol	-2.28	-1.48	-0.80
26	prednisolone heptanoate	-4.11	-1.04	-3.07
27	prednisolone octanoate	-3.96	-1.03	-2.93
28	prednisolone nonanoate	-4.04	-1.02	-3.02
29	prednisolone decanoate	-3.95	-1.00	-2.95
30	prednisolone pentadecanoate	-4.01	-1.00	-3.01
31	metoprolol	-2.56	-1.75	-0.81
32	nifedipine	-2.77	-1.18	-1.58
33	diclofenac sodium	-3.54	-2.26	-1.29
34	hydrocortisone	-3.92	-1.98	-1.94
35	hydrocortisone (azone)	-2.67	-1.98	-0.69
36	hydrocortisone (DPY)	-2.59	-1.98	-0.61
37	hydrocortisone (DPI)	-2.61	-1.98	-0.63
38	hydrocortisone (DMEA)	-2.81	-1.98	-0.83
39	hydrocortisone (DMEI)	-3.22	-1.98	-1.24

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp)- log K_p (Brown & Rossi) (cmh^{-1})
40	hydrocortisone (DDE)	-3.08	-1.98	-1.10
41	hydrocortisone (ND)	-3.13	-1.98	-1.15
42	atenolol	-1.52	-4.45	2.92

The following compounds were eliminated because they have molecular weights greater than 500. Mannitol has a log P value of -3.10 that lies outside the constraints.

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp)- log K_p (Brown & Rossi) (cmh^{-1})
1	prednisolone undecanoate	-3.83	-1.00	-2.82
2	prednisolone tridecanoate	-3.97	-1.00	-2.97
3	mannitol	-3.06	-5.41	2.34

3. Mouse skin – Predicted skin permeability using the Cronin et al. (1999) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp)- log K_p (Cronin) (cmh^{-1})
1	theophylline	-0.18	-4.38	4.20
2	5 fluorouracil	0.63	-1.59	2.22
3	bis (1-piperindyl) methyl 5FU	-1.96	-3.59	1.63
4	1,3 bis (4-morpholinyl) methyl 5FU	-1.37	-3.63	2.26
5	7-(dibutylamino) methyl theophylline	-2.46	-5.83	3.37
6	7-(piperindyl) methyl theophylline	-1.85	-5.38	3.52
7	progesterone	-1.12	-2.72	1.60
8	estradiol	-2.10	-3.06	0.96
9	hydrocortisone	-3.44	-4.89	1.44
10	ethanol	-2.57	-3.04	0.47
11	propanol	-2.37	-2.79	0.42
12	butanol	-2.06	-2.45	0.39
13	pentanol	-1.79	-2.18	0.39
14	hexanol	-1.50	-1.83	0.33
15	heptanol	-1.15	-1.68	0.53
16	octanol	-0.89	-1.38	0.49
17	methanol	-2.43	-3.20	0.77
18	fentanyl	-2.09	-2.43	0.34
19	estradiol	-1.80	-3.06	1.27
20	corticosterone	-3.10	-4.41	1.30
21	corticosterone (PVP/PBS)	-3.06	-4.41	1.34
22	atenolol	-0.55	-6.48	5.93
23	propranolol	-4.35	-4.94	0.59
24	propranolol HCL	-1.12	-4.95	3.82
25	oxprenolol	-2.28	-3.61	1.33
26	prednisolone heptanoate	-4.11	-4.06	-0.06
27	prednisolone octanoate	-3.96	-3.96	0.00
28	metoprolol	-2.56	-3.63	1.07
29	nifedipine	-2.77	-3.48	0.71
30	diclofenac sodium	-3.54	-4.74	1.19
31	hydrocortisone	-3.92	-4.89	0.96
32	hydrocortisone (azone)	-2.67	-4.89	2.22
33	hydrocortisone (DPY)	-2.59	-4.89	2.29
34	hydrocortisone (DPI)	-2.61	-4.89	2.28
35	hydrocortisone (DMEA)	-2.81	-4.89	2.08
36	hydrocortisone (DMEI)	-3.22	-4.89	1.66

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp)- log K_p (Cronin) (cmh^{-1})
37	hydrocortisone (DDE)	-3.08	-4.89	1.81
38	hydrocortisone (ND)	-3.13	-4.89	1.75
39	atenolol	-1.52	-6.47	4.95

The following compounds were eliminated because they have molecular weights greater than. Mannitol has a log P value of -3.10 which lies outside the constraints.

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp) – log K_p (Cronin) (cmh^{-1})
1	prednisolone nonanoate	-4.04	-3.90	-0.14
2	prednisolone decanoate	-3.95	-3.67	-0.29
3	prednisolone undecanoate	-3.83	-3.51	-0.32
4	prednisolone tridecanoate	-3.97	-3.43	-0.55
5	prednisolone pentadecanoate	-4.01	-3.13	-0.88
6	mannitol	-3.06	-6.59	3.53

Figure 1. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (pred) (cmh^{-1}) estimated by the Potts and Guy model.

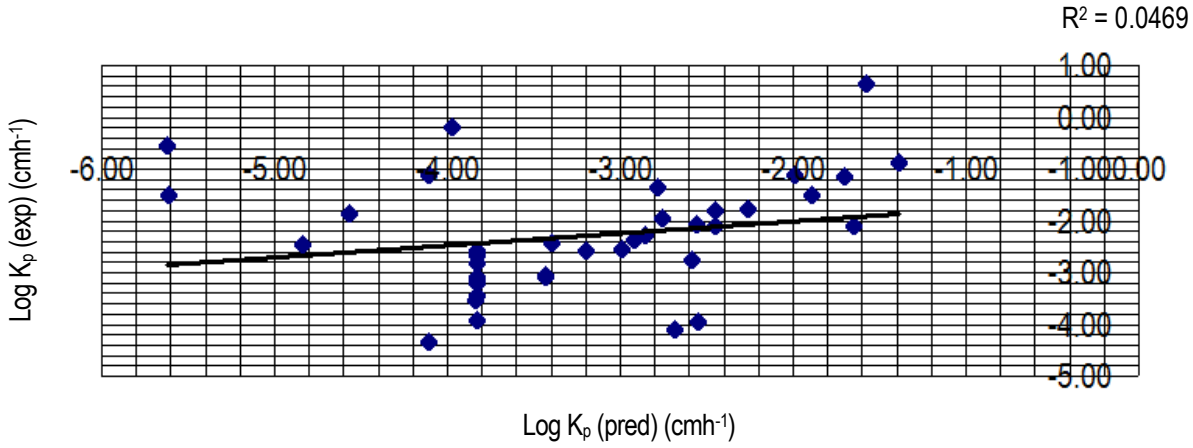


Figure 2. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (pred) (cmh^{-1}) estimated by the Cronin model.

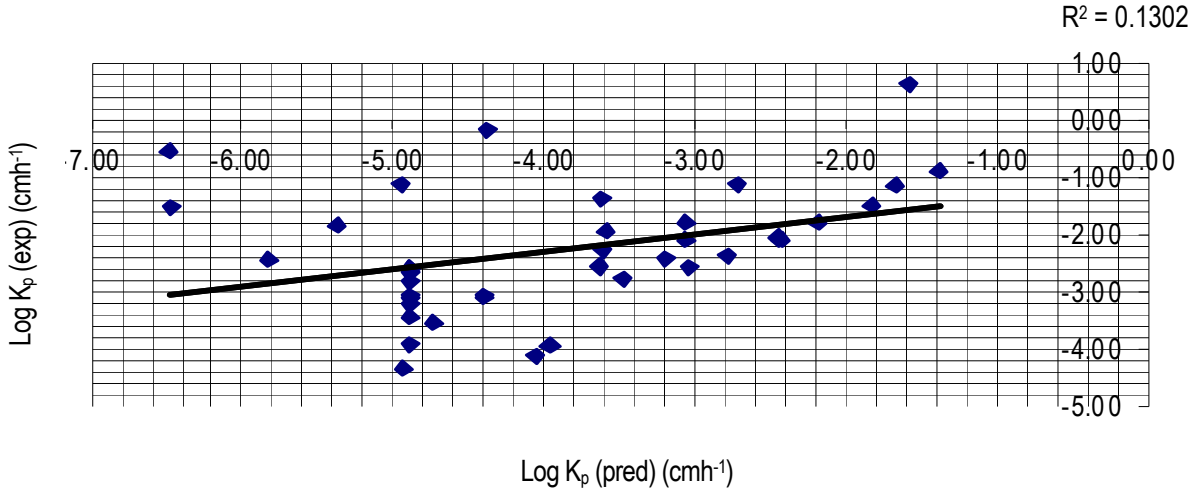
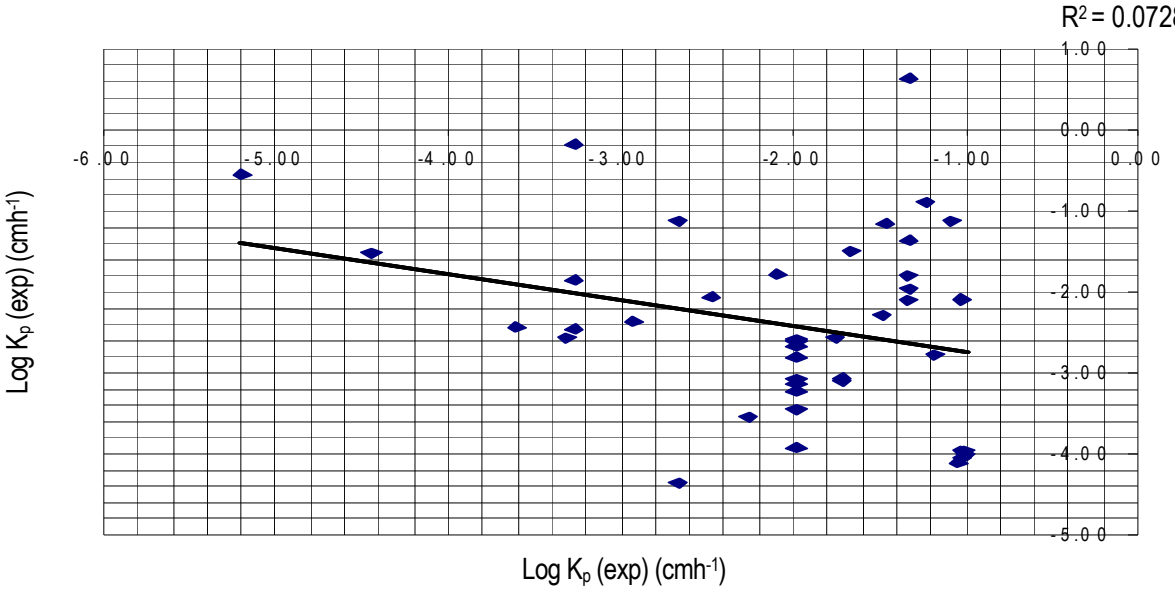


Figure 3. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (pred) (cmh^{-1}) estimated by the Brown and Rossi model.



Appendix 13 - Database B. Rat skin dataset – Experimental vs predicted K_p values

Rat skin dataset – Experimental permeability cofficients and drug properties

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	K_p (cmh^{-1})	Log K_p (cmh^{-1})
1	raffinose	504.00	-4.30 – a	18.73	0.00004	-4.42 – a
2	mannitol	182.00	-3.10 – a	18.53	0.00302	-2.52 – a
3	salicyclic acid	138.00	-2.14 – a	13.13	0.00012	-3.91 - a
4	atenolol	266.00	-1.77 – a	13.24	0.00045	-3.35 – a
5	pindolol	248.00	-0.33 – a	12.10	0.00037	-3.43 – a
6	metoprolol	267.00	0.03 – a	10.93	0.00017	-3.77 – a
7	alprenolol	249.00	0.65 – a	10.88	0.00447	-2.35 – a
8	aldosterone	360.04	1.08 – a	18.37	0.00013	-3.89 – a
9	corticosterone	347.00	1.94 – a	18.37	0.00135	-2.87 – a
10	testosterone	288.00	3.32 – a	10.87	0.04898	-1.31 – a
11	b-estradiol	272.00	3.86 – a	12.01	0.05888	-1.23 – a
12	b-estradiol	272.00	3.86 – b	12.01	0.09772	-1.01 – b
13	ibuprofen	206.30	3.51 – b	10.25	0.36308	-0.44 – b
14	flurbiprofen	244.30	4.12 – b	11.62	0.40738	-0.39 – b
15	indomethacin	357.80	3.08 – b	12.35	0.15136	-0.82 – b
16	morphine	285.30	0.62 – b	13.10	0.00046	-3.34 – b
17	hydrocortisone (azone)	326.47	1.53 – c	12.38	0.00132	-2.88 – c
18	hydrocortisone	326.47	1.53 – c	12.38	0.00012	-3.92 – c
19	hydrocortisone (DPY)	326.47	1.53 – c	12.38	0.00204	-2.69 – c
20	hydrocortisone (DPI)	326.47	1.53 – c	12.38	0.00178	-2.75 – c
21	hydrocortisone (DMEA)	326.47	1.53 – c	12.38	0.00069	-3.16 – c
22	hydrocortisone (DMEI)	326.47	1.53 – c	12.38	0.00076	-3.12 – c
23	hydrocortisone (DDE)	326.47	1.53 – c	12.38	0.00141	-2.85 – c
24	hydrocortisone (ND)	326.47	1.53 – c	12.38	0.00076	-3.27– c
25	aspirin	180.16	1.23 – d	11.81	0.00141	-0.46 – d
26	naproxen	230.26	3.18 – d	11.47	0.00054	-1.37 – d
27	flurbiprofen	244.26	3.86 – d	11.62	0.34674	-2.48 – d
28	nifedipine	346.30	3.14 – f	12.16	0.04266	-2.77 – f
29	5-fluorouracil	130.01	-0.86 – b	14.99	0.00331	-3.76 – b
30	barbital	184.20	0.65 – b	14.20	0.00170	-2.38 – b
31	sucrose	342.00	-3.70 – h	16.07	0.00174	-3.02 – g
32	5 - FU (SLS 1%)	130.01	-0.86 – e	14.99	0.00331	-2.37 – e
33	5 - FU (SLS 5%)	130.01	-0.86 – e	14.99	0.00170	-2.34 – e
34	indomethacin (SLS 1%)	357.86	3.08 – e	12.35	0.00017	-1.09 – e
35	propranolol	259.00	3.56 – f	11.96	0.00407	-2.39 – f
36	bufexamac	223.30	2.43 – d	13.33	0.26915	-0.57 – d

References

a - from Suhonen et al. (2003)
b - from Hatanaka et al. (1992)
c - from Fuhrman et al. (1997)
d - from Fang et al. (2003)
e - from Borras-Blasco et al. (1997)
f - from Diez et al. (1991)
g - from Peck et al. (1998)
h - from Johnson et al. (1997)

Predicted permeability coefficient(s) for rat skin using different models

1. Rat skin – Predicted skin permeability using the Potts and Guy (1992) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Potts & Guy) (cmh^{-1})	Log K_p (exp)- log K_p (Potts & Guy) (cmh^{-1})
1	salicyclic acid	-3.91	-5.06	1.15
2	atenolol	-3.35	-5.58	2.23
3	pindolol	-3.43	-4.45	1.02
4	metoprolol	-3.77	-4.30	0.54
5	alprenolol	-2.35	-3.76	1.41
6	aldosterone	-3.89	-4.13	0.24
7	corticosterone	-2.87	-3.44	0.57
8	testosterone	-1.31	-2.10	0.79
9	b-estradiol	-1.23	-1.62	0.39
10	b-estradiol	-1.01	-1.62	0.61
11	ibuprofen	-0.44	-1.47	1.03
12	fllurbiprofen	-0.39	-1.27	0.88
13	indomethacin	-0.82	-2.70	1.88
14	morphine	-3.34	-4.00	0.66
15	hydrocortisone (azone)	-2.88	-3.61	0.73
16	hydrocortisone	-3.92	-3.61	-0.31
17	hydrocortisone (DPY)	-2.69	-3.61	0.92
18	hydrocortisone (DPI)	-2.75	-3.61	0.86
19	hydrocortisone (DMEA)	-3.16	-3.61	0.45
20	hydrocortisone (DMEI)	-3.12	-3.61	0.49
21	hydrocortisone (DDE)	-2.85	-3.61	0.76
22	hydrocortisone (ND)	-3.12	-3.61	0.49
23	aspirin	-2.85	-2.93	0.08
24	naproxen	-3.27	-1.85	-1.42
25	flurbiprofen	-0.46	-1.45	0.99
26	nifedipine	-1.37	-2.58	1.21
27	5 - fuorouracil	-2.48	-4.10	1.62
28	barbital	-2.77	-3.36	0.59
29	5 - FU (SLS 1%)	-2.48	-4.10	1.62
30	5 - FU (SLS 5%)	-2.77	-4.10	1.33
31	indomethacin (SLS 1%)	-3.76	-2.70	-1.06
32	propranolol	-2.39	-1.75	-0.64
33	bufexamac	-0.57	-2.34	1.77

The following compounds have been excluded because they lie outside the constraints employed in this project.

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Potts & Guy) (cmh^{-1})	Log K_p (exp)- log K_p (Potts & Guy) (cmh^{-1})
1	raffinose	-4.42	-8.83	4.41
2	mannitol	-2.52	-6.01	3.49
3	sucrose	-2.76	-7.41	4.65

2. Rat skin – Predicted skin permeability using the Cronin et al. (1999) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp) - log K_p (Cronin) (cmh^{-1})
1	salicyclic acid	-3.91	-5.40	1.49
2	atenolol	-3.35	-6.43	3.08
3	pindolol	-3.43	-5.14	1.71

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp) - log K_p (Cronin) (cmh^{-1})
4	metoprolol	-3.77	-5.06	1.29
5	alprenolol	-2.35	-4.39	2.04
6	aldosterone	-3.89	-5.21	1.32
7	corticosterone	-2.87	-4.41	1.54
8	testosterone	-1.31	-2.74	1.43
9	b-estradiol	-1.23	-2.16	0.93
10	b-estradiol	-1.01	-2.16	1.15
11	ibuprofen	-0.44	-1.75	1.31
12	flurbiprofen	-0.39	-1.67	1.28
13	indomethacin	-0.82	-3.64	2.82
14	morphine	-3.34	-4.79	1.45
15	hydrocortisone (azone)	-2.88	-4.52	1.63
16	hydrocortisone	-3.92	-4.52	0.59
17	hydrocortisone (DPY)	-2.69	-4.52	1.82
18	hydrocortisone (DPI)	-2.75	-4.52	1.76
19	hydrocortisone (DMEA)	-3.16	-4.52	1.35
20	hydrocortisone (DMEI)	-3.12	-4.52	1.39
21	hydrocortisone (DDE)	-2.85	-4.52	1.66
22	hydrocortisone (ND)	-3.12	-4.52	1.39
23	aspirin	-2.85	-3.24	0.39
24	naproxen	-3.27	-2.25	-1.02
25	flurbiprofen	-0.46	-1.87	1.41
26	nifedipine	-1.37	-3.48	2.11
27	5 - fluorouracil	-2.48	-4.33	1.85
28	barbital	-2.77	-3.73	0.96
29	5 - FU (SLS 1%)	-2.48	-4.33	1.85
30	5 - FU (SLS 5%)	-2.77	-4.33	1.56
31	indomethacin (SLS 1%)	-3.76	-3.64	-0.12
32	propranolol	-2.39	-2.26	-0.13
33	bufexamac	-0.57	-2.76	2.19

Exclusions

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp) – log K_p (Cronin) (cmh^{-1})
1	raffinose	-4.42	-10.83	6.41
2	mannitol	-2.52	-6.59	4.07
3	sucrose	-2.76	-8.70	5.94

3. Rat skin – Predicted skin permeability using the revised Brown and Rossi (1995) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp)- log K_p (Brown & Rossi) (cmh^{-1})
1	salicyclic acid	-3.91	-4.69	0.78
2	atenolol	-3.35	-4.41	1.06
3	pindolol	-3.43	-3.33	-0.10
4	metoprolol	-3.77	-3.06	-0.71
5	alprenolol	-2.35	-2.60	0.25
6	aldosterone	-3.89	-2.29	-1.60
7	corticosterone	-2.87	-1.72	-1.15
8	testosterone	-1.31	-1.14	-0.17
9	b-estradiol	-1.23	-1.06	-0.17

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp)- log K_p (Brown & Rossi) (cmh^{-1})
10	b-estradiol	-1.01	-1.06	0.05
11	ibuprofen	-0.44	-1.11	0.67
12	flurbiprofen	-0.39	-1.04	0.65
13	indomethacin	-0.82	-1.20	0.38
14	morphine	-3.34	-2.62	-0.72
15	hydrocortisone (azone)	-2.88	-1.98	-0.90
16	hydrocortisone	-3.92	-1.98	-1.94
17	hydrocortisone (DPY)	-2.69	-1.98	-0.71
18	hydrocortisone (DPI)	-2.75	-1.98	-0.77
19	hydrocortisone (DMEA)	-3.16	-1.98	-1.18
20	hydrocortisone (DMEI)	-3.12	-1.98	-1.14
21	hydrocortisone (DDE)	-2.85	-1.98	-0.87
22	hydrocortisone (ND)	-3.12	-1.98	-1.14
23	aspirin	-2.85	-2.19	-0.66
24	naproxen	-3.27	-1.17	-2.10
25	flurbiprofen	-0.46	-1.06	0.60
26	nifedipine	-1.37	-1.18	-0.19
27	5 - fluorouracil	-2.48	-3.73	1.25
28	barbital	-2.77	-2.60	-0.17
29	5 - FU (SLS 1%)	-2.48	-3.73	1.25
30	5 - FU (SLS 5%)	-2.77	-3.73	0.90
31	indomethacin (SLS 1%)	-3.76	-1.20	-2.56
32	propranolol	-2.39	-1.10	-1.29
33	bufexamac	-0.57	-1.45	0.88

Exclusions

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp)- log K_p (Brown & Rossi) (cmh^{-1})
1	raffinose	-4.42	-6.30	1.88
2	mannitol	-2.52	-5.40	2.88
3	sucrose	-2.76	-5.87	3.11

Figure 1. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (pred) (cmh^{-1}) estimated by the Potts and Guy model.

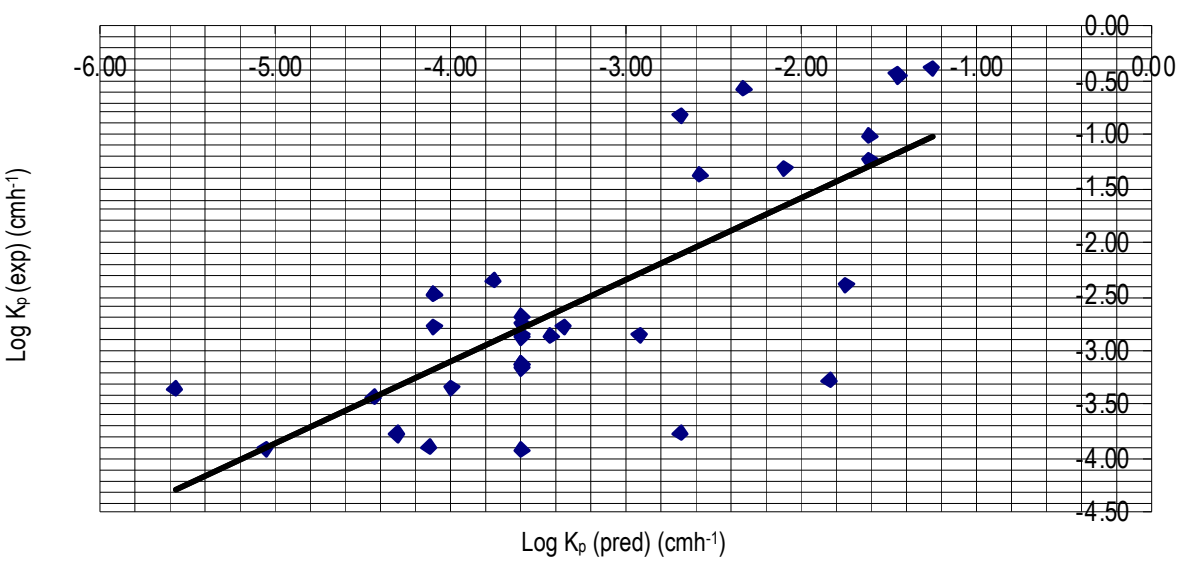


Figure 2. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (pred) (cmh^{-1}) estimated by the Cronin model.

$R^2 = 0.59368$

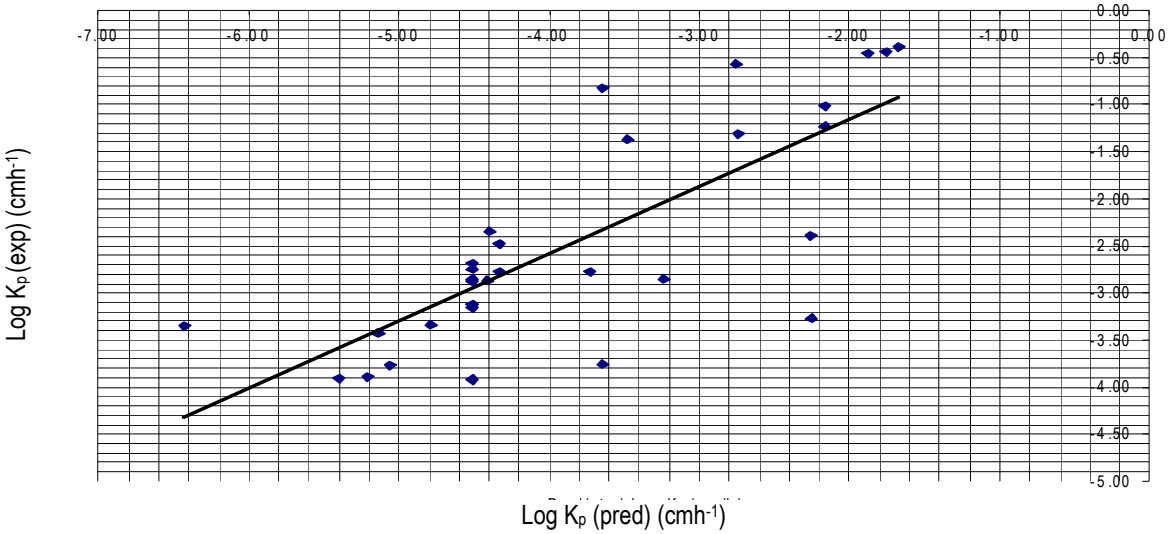
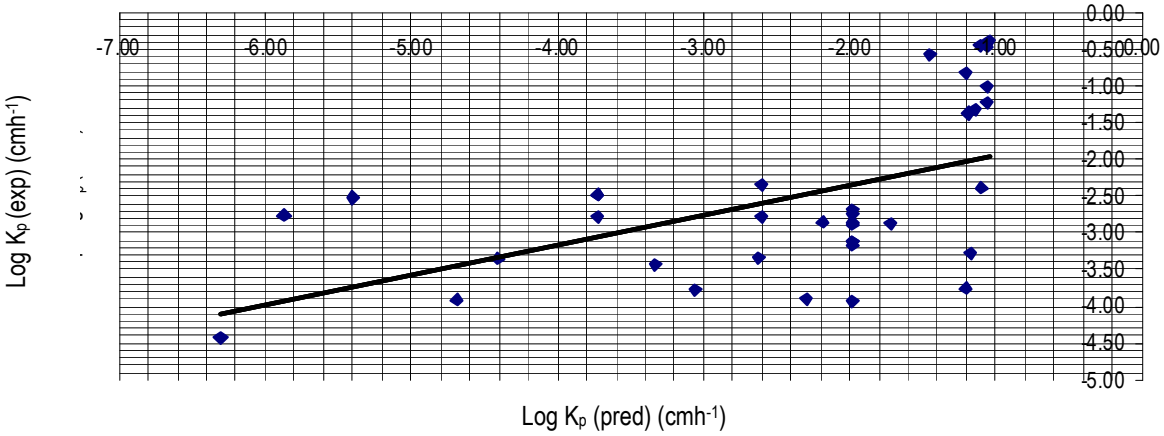


Figure 3. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (pred) (cmh^{-1}) estimated by the Brown and Rossi model.

$R^2 = 0.27376$



Appendix 14. Database B. Silicone membrane dataset – Experimental vs predicted K_p values

Silicone membrane dataset – Experimental permeability coefficients and drug properties

No	Name	MW	Log P KOWWIN	SP $(cal/cm^3)^{1/2}$	K_p (cmh^{-1})	Log K_p (cmh^{-1})
1	estradiol	272.40	2.69 - a	12.01	0.262080	-0.58 – a
2	ibuprofen	206.30	3.51 – a	10.25	12.63600	1.10 – a
3	flurbiprofen	244.30	3.86 – a	11.62	2.642400	0.42 – a
4	indomethacin	357.80	3.09 – a	12.35	0.063000	-1.20 – a
5	barbital	184.20	0.87 – a	14.20	0.002690	-2.57 – a
6	5 - fluorouracil	130.01	-0.86 – a	14.99	0.000004	-5.37 – a
7	benzoic acid	122.10	1.88 – b	12.70	0.057000	-1.24 – b
8	salicyclic acid	138.10	2.26 – b	13.13	0.160000	-0.80 – b
9	phenol	94.11	1.49 – c	13.46	0.129000	-0.89 – c
10	diazepam	284.75	2.92 – c	11.52	0.450000	-0.35 – c
11	2-nitrophenol	139.11	1.79 – c	13.19	1.233000	0.09 – c
12	3-nitrophenol	139.11	2.00 – c	13.19	0.045000	-1.35 – c
13	4-nitrophenol	139.11	1.91 – c	13.19	0.030000	-1.52 – c
14	nitrobenzene	123.11	1.85 – c	10.45	2.009000	0.30 – c
15	2-bromophenol	173.02	2.35 – c	15.17	0.701000	-0.15 – c
16	4-bromophenol	173.02	2.59 – c	15.17	0.360000	-0.44 – c
17	hydrocortisone	362.50	1.53 – b	12.38	0.000074	-4.13 – d
18	hydrocortisone -21- hexanoate	460.61	4.48 – b	11.01	0.001480	-2.83 - d

References
a - from Hatanaka et al. (1992)
b - from the Flynn database (1990)
c - from Geinoz et al. (2002)
d - from Hagen et al. (1987)

Predicted permeability coefficient(s) for silicone membrane using different models

1. Silicone membrane – Predicted permeability coefficient(s) using the Potts and Guy (1992) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Potts & Guy) (cmh^{-1})	Log K_p (exp) – log K_p (Potts & Guy) (cmh^{-1})
1	estradiol	-0.58	-2.45	1.87
2	ibuprofen	1.10	-1.47	2.57
3	flurbiprofen	0.42	-1.45	1.87
4	indomethacin	-1.20	-2.69	1.49
5	barbital	-2.57	-3.21	0.64
6	5 - fluorouracil	-5.37	-4.10	-1.26
7	benzoic acid	-1.24	-2.11	0.87
8	salicyclic acid	-0.80	-1.94	1.14
9	phenol	-0.89	-2.22	1.33
10	diazepam	-0.35	-2.36	2.02
11	2-nitrophenol	0.09	-2.28	2.37
12	3-nitrophenol	-1.35	-2.13	0.78
13	4-nitrophenol	-1.52	-2.19	0.67
14	nitrobenzene	0.30	-2.14	2.44
15	2-bromophenol	-0.15	-2.09	1.93
16	4-bromophenol	-0.44	-1.92	1.47
17	hydrocortisone	-4.13	-3.82	-0.31
18	hydrocortisone -21- hexanoate	-2.83	-2.33	-0.50

2. Silicone membrane – Predicted permeability coefficient(s) using the revised Robinson (1995) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Robinson) (cmh^{-1})	Log K_p (exp)- log K_p (Robinson) (cmh^{-1})
1	estradiol	-0.58	-2.64	2.06
2	ibuprofen	1.10	-1.79	2.89
3	flurbiprofen	0.42	-1.81	2.23
4	indomethacin	-1.20	-2.82	1.62
5	barbital	-2.57	-3.21	0.64
6	5 - fluorouracil	-5.37	-2.88	-2.48
7	benzoic acid	-1.24	-2.17	0.92
8	salicyclic acid	-0.80	-2.06	1.27
9	phenol	-0.89	-2.16	1.27
10	diazepam	-0.35	-2.57	2.22
11	2-nitrophenol	0.09	-2.35	2.44
12	3-nitrophenol	-1.35	-2.22	0.88
13	4-nitrophenol	-1.52	-2.28	0.76
14	nitrobenzene	0.30	-2.19	2.49
15	2-bromophenol	-0.15	-2.25	2.10
16	4-bromophenol	-0.44	-2.11	1.67
17	hydrocortisone	-4.13	-3.77	-0.36
18	hydrocortisone -21- hexanoate	-2.83	-2.44	-0.39

3. Silicone membrane – Predicted permeability coefficient(s) using the revised Brown and Rossi (1995) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp)- log K_p (Brown & Rossi) (cmh^{-1})
1	estradiol	-0.58	-1.33	0.75
2	ibuprofen	1.10	-1.11	2.21
3	flurbiprofen	0.42	-1.06	1.48
4	indomethacin	-1.20	-1.20	-0.00
5	barbital	-2.57	-2.44	-0.13
6	5 - fluorouracil	-5.37	-3.72	-1.65
7	benzoic acid	-1.24	-1.75	0.51
8	salicyclic acid	-0.80	-1.53	0.74
9	phenol	-0.89	-2.01	1.12
10	diazepam	-0.35	-1.25	0.90
11	2-nitrophenol	0.09	-1.81	1.90
12	3-nitrophenol	-1.35	-1.68	0.33
13	4-nitrophenol	-1.52	-1.74	0.21
14	nitrobenzene	0.30	-1.77	2.08
15	2-bromophenol	-0.15	-1.49	1.33
16	4-bromophenol	-0.44	-1.37	0.93
17	hydrocortisone	-4.13	-1.98	-2.15
18	hydrocortisone -21- hexanoate	-2.83	-1.02	-1.81

4. Silicone membrane – Predicted permeability coefficient(s) using the Cronin et al. (1999) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp)- log K_p (Cronin) (cmh^{-1})
1	estradiol	-0.58	-3.06	2.48
2	ibuprofen	1.10	-1.75	2.85
3	flurbiprofen	0.42	-1.87	2.30
4	indomethacin	-1.20	-3.64	2.44
5	barbital	-2.57	-3.56	0.99

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp)- log K_p (Cronin) (cmh^{-1})
6	5 - fluorouracil	-5.37	-4.33	-1.04
7	benzoic acid	-1.24	-2.14	0.90
8	salicyclic acid	-0.80	-2.01	1.22
9	phenol	-0.89	-2.15	1.26
10	diazepam	-0.35	-3.01	2.67
11	2-nitrophenol	0.09	-2.38	2.48
12	3-nitrophenol	-1.35	-2.22	0.88
13	4-nitrophenol	-1.52	-2.29	0.77
14	nitrobenzene	0.30	-2.17	2.48
15	2-bromophenol	-0.15	-2.30	2.15
16	4-bromophenol	-0.44	-2.11	1.67
17	hydrocortisone	-4.13	-4.89	0.75
18	hydrocortisone -21- hexanoate	-2.83	-3.62	0.79

Figure 1. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (pred) (cmh^{-1}) estimated by the Cronin model.

$R^2 = 0.704$

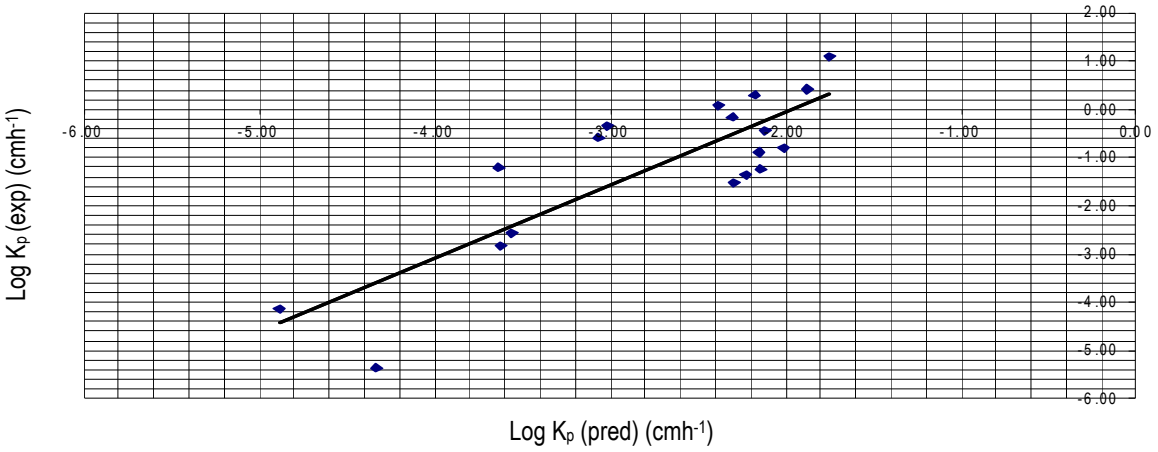


Figure 2. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (pred) (cmh^{-1}) estimated by the Potts and Guy model.

$R^2 = 0.7936$

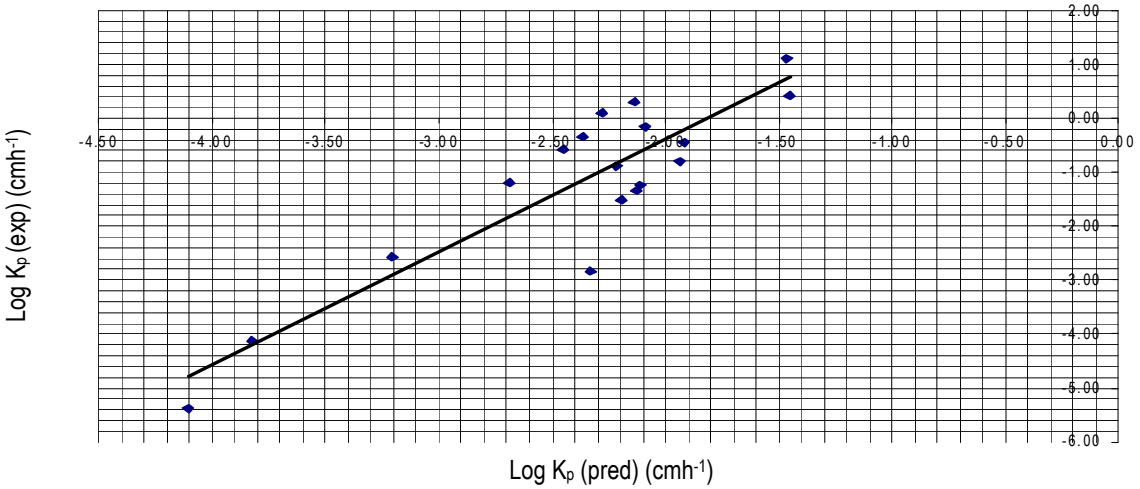


Figure 3. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (pred) (cmh^{-1}) estimated by the Robinson model.

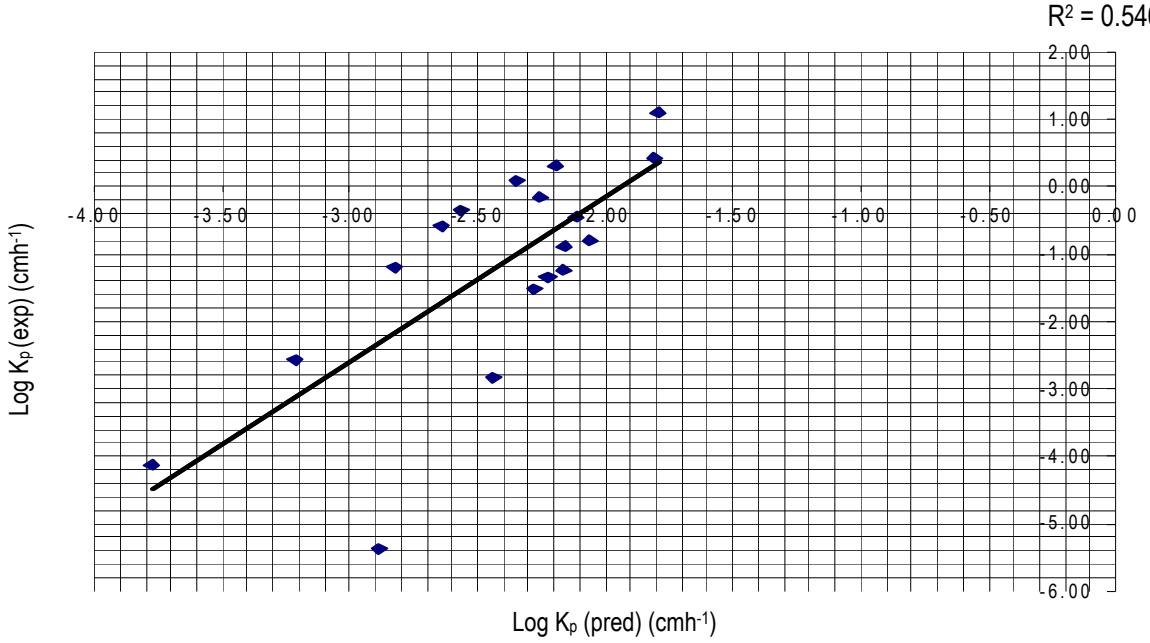
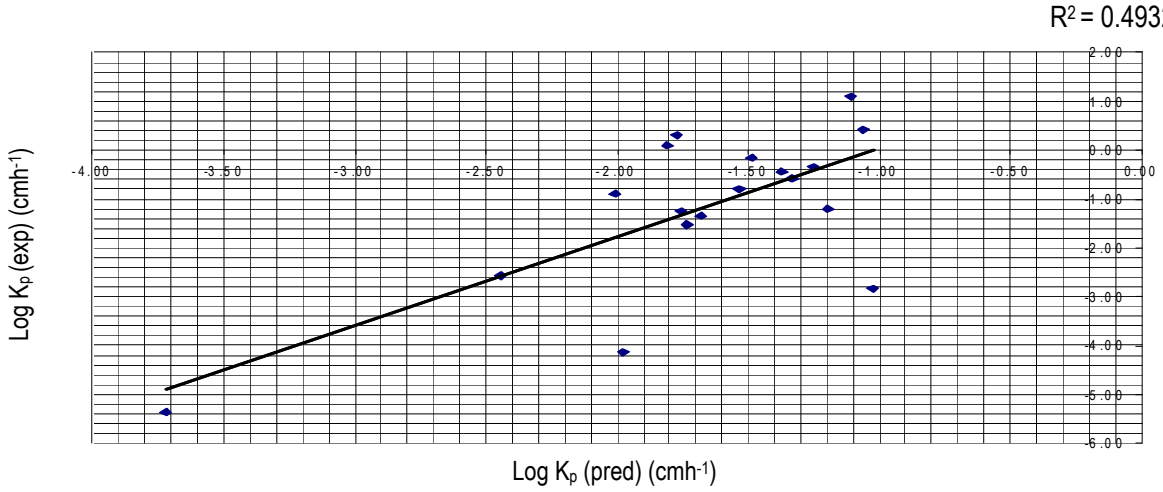


Figure 4. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (pred) (cmh^{-1}) estimated by the Brown and Rossi model.



Appendix 15. Database C. Human skin dataset – Experimental vs predicted K_p values

Human skin dataset – Experimental permeability coefficients and drug properties

No	Name	MW	MPt (°C)	Log P KOWWIN	Log K_p(exp) (cmh^{-1})	Journal
1	paraquat	257.16	180.00	-2.71	-5.06	*J. Investig.Dermatol*. 96, 921-925
2	water	18.02	0.00	-1.38	-3.15	*Toxicol.Vitro* 8, 827-830
3	methotrexate	454.45	195.00	-1.28	-3.95	*Int. J.Pharm*. 25, 65-75
4	n-nitrosodiethanolamine	134.13	81.52	-1.28	-2.39	*Food Chem.Toxicol*.33, 315-322
5	2-(2-methoxyethoxy) ethanol	120.15	-70.00	-1.18	-3.69	*Environ.Health Perspect*. 57, 193-197
6	adenosine	267.24	234.00	-1.05	-3.88	*Eur.J.Pharm.Sci*. 2006
7	dimethylformamide	73.10	-61.00	-0.93	-2.02	*Occup. Hyg*. 1, 191-198
8	5-fluorouracil	130.01	281.00	-0.81	-4.78	*J.Investig.Pharmacol*. 94, 235-240
9	etodolac	287.26	146.50	-0.77	-2.13	*J.Pharm.Science* 92:3, 656-664
10	methanol	32.04	-98.00	-0.77	-2.80	*Int. J.Pharm*. 18, 299-309
11	2-(2-ethoxyethoxy)ethanol	134.18	-76.00	-0.69	-3.88	*Environ.Health Perspect*. 57, 193-197
12	famotidine	337.43	163.50	-0.64	-4.79	*J.Pharm.Science* 92:3, 656-664
13	nikel	58.70	14.53	-0.57	-3.21	*Toxicology Letters* 170 (2007), 49-56
14	deoxyadenosine	251.24	187.00	-0.55	-3.89	*Eur.J.Pharm.Sci*. 2006
15	1-methoxylpropan-2-ol	90.12	-142.00	-0.49	-3.19	Int.Arch.Occup.Env.Health 75, 519-527
16	squaric acid	114.06	293.00	-0.44	-5.12	*Arch.Dermatol.Res*. 280, 57-60
17	nizatidine	331.45	130.00	-0.43	-4.43	*J.Pharm.Science* 92:3, 656-664
18	2-ethoxyethanol	90.12	-90.00	-0.42	-3.07	*Environ.Health Perspect*. 57, 193-197
19	theophylline	180.17	273.00	-0.39	-3.36	*J.Soc.Cosmet.Chem*. 40, 231-242
20	boric acid	61.83	171.00	-0.22	-3.30	*Toxicol.Sci*. 45, 42-51
21	atenolol	266.30	147.00	-0.03	-4.30	*Int.J.Pharm*. 194, 249-259
22	caffeine	194.20	238.00	0.16	-3.68	*J.Dermatol*. 115, 1-11
23	2-(2-butoxyethoxy)ethanol	162.23	-68.00	0.29	-4.45	*Environ.Health Perspect*. 57, 193-197
24	ranitidine	314.10	133.00	0.29	-4.05	*J.Pharm.Science* 92:3, 656-664
25	cimetidine	252.34	142.00	0.40	-4.42	*Eur.J.Pharm.Sci*. 2006
26	nicorandil	211.18	92.50	0.43	-4.30	*Eur.J.Pharm. Sci*. 11, 59-68
27	2-butoxyethanol	118.18	-70.00	0.57	-3.67	*Environ.Health Perspect*. 57, 193-197
28	2-ethoxyethyl acetate	132.16	-61.70	0.59	-3.09	*Environ.Health Perspect*. 57, 193-197
29	methyl nicotinate	137.14	42.50	0.64	-2.47	*J.Pharm.Sci*. 80, 54-56
30	nicotinic acid	123.11	236.60	0.69	-4.62	*J.Pharm.Sci*. 80, 104-107
31	morphine	285.30	255.00	0.72	-5.03	*Pharmaceut.Res*. 6, 825-832
32	isosorbide dinitrate (ISDN)	236.14	70.00	0.76	-2.35	*Eur.J.Pharm. Sci*. 11, 59-68
33	2,4 dimethylamine	266.13	86.00	0.84	-3.09	*Toxicol.Vitro*11, 251-262
34	1,6-hexanediol diglycidyl ether (HDDGE)	230.20	84.83	0.84	-3.87	*Xenobiotica* 30, 469-483
35	nicotine	162.30	-7.90	1.00	-1.99	*Eur.J.Pharm. Sci*. 11, 59-68
36	hydroquinone	110.11	170.00	1.03	-5.03	*Food Chem.Toxicol*. 35, 1009-1016
37	resorcinol	110.11	110.00	1.03	-3.62	*J.Pharm.Pharmacol*. 29, 677-683
38	aniline	93.00	-6.20	1.08	-1.21	*I.J.Pharmac*. 129, 33-40
39	2-phenoxyethanol	138.17	14.00	1.10	-2.87	*Food Chem.Toxicol*. 35, 1009-1016
40	ethyl nicotinate	151.17	-8.50	1.13	-2.22	*J.Pharm.Sci*. 80, 54-56
41	codeine	299.40	155.00	1.28	-4.31	*Pharmaceut.Res*. 6, 825-832
42	naltrexone (NTX)	341.00	166.00	1.39	-2.02	*J.Pharm.Sci*. 91, 2571-2578
43	pirimicarb	238.29	254.60	1.40	-2.57	*Ann.Occup.Hyg*. 48, 697-701
44	prednisone	358.44	492.40	1.46	-4.61	*Biol.Pharm.Bull*. 29 (11), 2270-2273
45	NTX-3-acetate (ACE-NTX)	383.00	114.00	1.47	-2.11	*J.Pharm.Sci*. 91, 2571-2578
46	prednisolone	360.44	480.70	1.49	-4.63	*Biol.Pharm.Bull*. 29 (11), 2270-2273
47	coumarin	146.15	70.60	1.51	-2.04	*Meth.and Find Exp.Clin.Pharmac*.11,643-646
48	phenol	94.11	40.90	1.51	-2.09	*J.Pharm.Pharmacol*. 29, 677-683
49	2-phenylethanol	122.20	-27.00	1.57	-1.51	*I.J.Pharmac*. 129, 33-40
50	hydromorphone	285.34	266.00	1.60	-4.82	*Pharm.Res*. 6, 825-832
51	hydrocortisone	362.50	220.00	1.61	-3.80	*J.Contr.Release,* 76, 327-335
52	aldosterone	360.45	164.00	1.63	-4.24	*J.Pharm.Sci*. 84, 1144-1146

No	Name	MW	MPt (°C)	Log P KOWWIN	Log K_p(exp) (cmh^{-1})	Journal
53	lidocaine	234.34	67.00	1.66	-1.97	*Int. J.Pharm.* 71,167-173
54	metoprolol	267.40	124.00	1.69	-3.08	*Int.J.Pharm.* 194, 249-259
55	cortisone	360.50	220.00	1.81	-5.00	*J.Investig.Dermatol.* 52, 63-70
56	oxprenolol	265.40	110.00	1.83	-2.81	*Int.J.Pharm.* 194, 249-259
57	bisoprolol	325.50	100.00	1.84	-3.57	*Int.J.Pharm.* 173,141-148
58	estrone	270.40	254.50	1.85	-2.44	*J.Investig.Dermatol.* 52, 63-70
59	ITF 296	238.00	55.50	1.85	-2.45	*Eur.J.Pharm. Sci.* 11, 59-68
60	benzoic acid	122.10	122.40	1.87	-2.88	*J.Pharm.Sci.* 85, 249-252
61	propoxur	209.25	87.00	1.90	-3.05	*Toxicol.Sci.* 58, 15-22
62	3-nitrophenol	139.10	98.00	1.91	-2.25	*J.Pharm.Pharmacol.* 29, 677-683
63	griseofulvin	352.77	220.00	1.92	-2.71	*Meth.and Find Exp.Clin.Pharmac.*11,643-646
64	celiprolol	379.50	111.00	1.93	-3.23	*Int.J.Pharm.* 173, 141-148
65	NTX-3-propionate (PROP-NTX)	397.00	147.00	1.96	-2.60	*J.Pharm.Sci.* 91, 2571-2578
66	benzene	78.12	5.50	1.99	-0.95	*J.Invest.Dermatol.* 85, 522-526
67	corticosterone	346.50	183.00	1.99	-4.22	*J.Investig.Dermatol.* 52, 63-70
68	methyl-4-hydroxy benzoate	152.14	131.00	2.00	-2.32	*J.Soc.Cosmet.Chem.*40, 231-242
69	betamethasone	392.45	512.20	2.02	-5.70	*Biol.Pharm.Bull.* 29 (11), 2270-2273
70	2-cresol (o-cresol)	108.10	30.90	2.06	-1.80	*J.Pharm.Pharmacol.* 29, 677-683
71	3-cresol (m-cresol)	108.14	11.50	2.06	-1.82	*J.Pharm.Pharmacol.* 29, 677-683
72	4-cresol (p-cresol)	108.10	33.00	2.06	-1.76	*J.Pharm.Pharmacol.* 29, 677-683
73	butyl nicotinate	179.22	69.59	2.11	-1.78	*J.Pharm.Sci.* 80, 54-56
74	ethylaniline	121.20	-64.00	2.11	-0.54	*I.J.Pharmac.* 129, 33-40
75	o-cresyl glycidyl ether (oCGE)	164.20	30.25	2.16	-4.03	*Xenobiotica* 30, 469-483
76	nimesulide	308.31	143.00	2.22	-3.00	*J.Pharm.Science* 92:3, 656-664
77	salicylic acid	138.10	158.00	2.24	-1.89	*Eur.J.Pharm.Sci.* 11, 59-68
78	N-N-diethyl m-toluamide	191.28	-45.00	2.26	-2.65	*Toxicol.Vitro* 7,141-148
79	malathion	330.36	2.85	2.29	-0.69	*Food Chem.Toxicol.* 34, 731-735
80	benzyl nicotinate	213.24	24.00	2.35	-1.80	*J.Pharm.Sci.* 80, 54-56
81	4-bromophenol	173.01	66.40	2.40	-1.44	*J.Pharm.Pharmacol.* 29, 677-683
82	estriol	288.40	282.00	2.41	-4.40	*J.Investig.Dermatol.* 52, 63-70
83	methyl paraben	152.15	not avail.	2.00	-2.38	*Eur.J.Pharm.Sci.* 21, 337-345
84	dibutyl squarate	226.27	176.70	2.45	-4.70	*Arch.Dermatol.Res.* 280, 57-60
85	NTX-3-butyrate (BUT-NTX)	411.00	106.00	2.45	-2.89	*J.Pharm.Sci.* 91, 2571-2578
86	NTX-3-valerate (VAL-NTX)	425.00	83.00	2.45	-3.15	*J.Pharm.Sci.* 91, 2571-2578
87	triclosan	289.55	265.60	2.47	-4.47	*Int.J.Pharm.* 235, 229-236
88	4-phenylbutanol	150.00	16.20	2.55	-1.06	*I.J.Pharmac.*129, 33-40
89	propranolol	295.30	166.00	2.60	-2.75	*Int.J.Pharm.* 194, 249-259
90	3,4 xylenol	202.55	62.50	2.61	-1.44	*J.Pharm.Pharmacol.* 29, 677-683
91	DEP	222.24	-3.00	2.65	-4.94	*Environ.Health Perspect.* 74, 223-227
92	2-naphthol	144.16	123.00	2.69	-1.55	*J.Pharm.Pharmacol.* 29, 677-683
93	methyl parathion	263.21	35.50	2.75	-4.42	*Occup.Environ.Med.* 54, 524-525
94	androstedione	288.42	260.00	2.75	-2.91	*Biol.Pharm.Bull.* 29 (11), 2270-2273
95	n-octanol	130.23	-15.50	2.81	-1.21	*Int.J.Pharm.* 18, 299-309
96	methiocarb	225.31	119.00	2.87	-2.96	*Ann.Occup.Hyg.* 48, 697-701
97	NTX-3-hexanoate (HEX-NTX)	439.00	62.00	2.94	-2.92	*J.Pharm.Sci.* 91, 2571-2578
98	meperidine	247.40	270.00	3.03	-2.43	*Pharm.Res.* 6, 825-832
99	4-n-butylaniline	149.24	-14.00	3.10	-0.39	*I.J.Pharmac.* 129, 33-40
100	n-hexyl nicotinate	207.27	not avail.	3.10	-1.75	*J.Pharm.Sci.* 80, 54-56
101	naproxene	230.30	153.00	3.10	-2.54	*Int.J.Pharm.* 170, 129-133
102	ethanol	46.07	-114.10	3.12	-3.50	*J.Investig.Dermatol.* 96, 921-925
103	ketoprofen	254.29	94.00	3.12	-3.21	*J.Pharm.Science* 92:3, 656-664
104	cortexolone	346.47	208.00	3.15	-4.12	*J.Investig.Dermatol.* 52, 63-70
105	chloroxylenol	156.60	115.00	3.25	-1.23	*J.Pharm.Pharmacol.* 29, 677-683
106	testosterone	288.40	155.00	3.27	-2.17	*J.Dermatol.* 115, 1-11
107	2-phenylphenol	170.21	116.10	3.28	-1.74	*Regul.Toxicol.Pharmacol.* 35, 198-208

No	Name	MW	MPt (°C)	Log P KOWWIN	Log K_p(exp) (cmh^{-1})	Journal
108	butyl paraben	194.23	68.50	3.47	-1.00	*Eur.J.Pharm.Sci.* 21, 337-345
109	thymol	150.20	49.00	3.52	-1.28	*J.Pharm.Pharmacol.* 29, 677-683
110	4-n-pentylaniline	163.30	not avail.	3.59	-0.65	*I.J.Pharmac.* 129, 33-40
111	sufentanil	386.60	97.00	3.62	-1.92	*Pharm.Res.* 6, 825-832
112	progesterone	314.50	121.00	3.67	-1.52	*J.Pharm.Sci.* 84, 1144-1146
113	parathion	291.26	6.10	3.73	-3.72	*Toxicol.Appl.Pharmacol.* 168,149-152
114	bisphenol A diglycidyl ether (BADGE)	340.80	10.00	3.84	-6.32	*Xenobiotica* 30, 469-483
115	diazinon	304.35	88.00	3.86	-2.02	*Toxicol.Vitro* 8, 1219-1224
116	pregnenolone	316.50	192.00	3.89	-2.82	*J.Investig.Dermatol.* 52, 63-70
117	NTX-3 heptanoate (HEP-NTX)	453.00	58.00	3.92	-3.05	*J.Pharm.Sci.* 91, 2571-2578
118	b-estradiol	272.40	173.00	3.97	-2.00	*Pharm.Res.* 10, 1745-1750
119	ibuprofen	206.30	76.00	3.97	-1.44	*Int.J.Pharm.* 170, 129-133
120	ethinyl estradiol	296.40	285.00	4.00	-4.43	*Biol.Pharm.Bull.* 29 (11), 2270-2273
121	dichlofenac	296.16	337.50	4.02	-3.00	*Int.J.Pharm.* 170, 129-133
122	doxycycline HCL	444.44	866.00	4.05	-5.32	*Int.Journal of Pharm.* 190, 155-164
123	fentanyl	336.5	84.00	4.05	-2.25	*Pharm.Res.* 6, 825-832
124	diethyl squarate	170.16	131.60	4.07	-3.92	*Arch.Dermatol.Res.* 280, 57-60
125	prochloraz	376.70	48.00	4.13	-3.15	*Ann.Occup.Hyg.* 48, 697-701
126	lindane	290.83	112.50	4.26	-5.23	*Hum.Exp.Toxicol.* 16, 652-657
127	chlorpyrifos	350.59	42.00	4.66	-3.60	*Hum.Exp.Toxicol.*19, 104-107
128	nonane	128.30	-53.50	4.76	-4.38	*Toxicol. Sci.* 55, 247-255
129	flufenamic acid	281.20	133.00	4.88	-3.26	*J.Contr.Rel.* 75, 283-295

Predicted permeability coefficient(s) for human skin using different models

1. Human skin – Predicted permeability using the Potts and Guy (1992) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Potts & Guy) (cmh^{-1})	Log K_p (exp)- log K_p (Potts & Guy) (cmh^{-1})
1	paraquat	-5.06	-6.19	-1.13
2	water	-3.15	-3.79	-0.64
3	methotrexate	-3.95	-6.38	-2.43
4	n-nitrosodiethanolamine	-2.39	-4.43	-2.04
5	2-(2-methoxyethoxy)ethanol	-3.69	-4.27	-0.58
6	adenosine	-3.88	-5.08	-1.20
7	dimethylformamide	-2.02	-3.81	-1.79
8	5-fluorouracil	-4.78	-4.07	0.71
9	etodolac	-2.13	-5.00	-2.87
10	methanol	-2.80	-3.44	-0.64
11	2-(2-ethoxyethoxy)ethanol	-3.88	-4.01	-0.13
12	famotidine	-4.79	-5.21	-0.42
13	nikel	-3.21	-3.46	-0.25
14	deoxyadenosine	-3.89	-4.62	-0.73
15	1-methoxylpropan-2-ol	-3.19	-3.60	-0.41
16	squaric acid	-5.12	-3.71	1.41
17	nizatidine	-4.43	-5.03	-0.60
18	2-ethoxyethanol	-3.07	-3.55	-0.48
19	theophylline	-3.36	-4.08	-0.72
20	boric acid	-3.30	-3.23	0.07
21	atenolol	-4.30	-4.35	-0.05
22	caffeine	-3.68	-3.77	-0.09
23	2-(2-butoxyethoxy)ethanol	-4.45	-3.48	0.97
24	ranitidine	-4.05	-4.41	-0.36
25	cimetidine	-4.42	-3.96	0.46

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Potts & Guy) (cmh^{-1})	Log K_p (exp)- log K_p (Potts & Guy) (cmh^{-1})
26	nicorandil	-4.30	-3.68	0.62
27	2-butoxyethanol	-3.67	-3.02	0.65
28	2-ethoxyethyl acetate	-3.09	-3.09	0.00
29	methyl nicotinate	-2.47	-3.08	-0.61
30	nicotinic acid	-4.62	-2.96	1.66
31	morphine	-5.03	-3.93	1.10
32	isosorbide dinitrate (ISDN)	-2.35	-3.60	-1.25
33	2,4 dimethylamine	-3.09	-3.73	-0.64
34	1,6-hexanediol diglycidyl ether (HDDGE)	-3.87	-3.51	0.36
35	nicotine	-1.99	-2.98	-0.99
36	hydroquinone	-5.03	-2.64	2.39
37	resorcinol	-3.62	-2.64	0.98
38	aniline	-1.21	-2.50	-1.29
39	2-phenoxyethanol	-2.87	-2.76	0.11
40	ethyl nicotinate	-2.22	-2.82	-0.60
41	codeine	-4.31	-3.62	0.69
42	naltrexone (NTX)	-2.02	-3.79	-1.77
43	pirimicarb	-2.57	-3.16	-0.59
44	prednisone	-4.61	-3.85	0.76
45	NTX-3-acetate (ACE-NTX)	-2.11	-3.99	-1.88
46	prednisolone	-4.63	-3.84	0.79
47	coumarin	-2.04	-2.52	-0.48
48	phenol	-2.09	-2.20	-0.11
49	2-phenylethanol	-1.51	-2.33	-0.82
50	hydromorphone	-4.82	-3.30	1.52
51	hydrocortisone	-3.80	-3.77	0.03
52	aldosterone	-4.24	-3.74	0.50
53	lidocaine	-1.97	-2.95	-0.98
54	metoprolol	-3.08	-3.13	-0.05
55	cortisone	-5.00	-3.61	1.39
56	oxprenolol	-2.81	-3.02	-0.21
57	bisoprolol	-3.57	-3.38	0.19
58	estrone	-2.44	-3.04	-0.60
59	ITF 296	-2.45	-2.84	-0.39
60	benzoic acid	-2.88	-2.12	0.76
61	propoxur	-3.05	-2.63	0.42
62	3-nitrophenol	-2.25	-2.19	0.06
63	griseofulvin	-2.71	-3.49	-0.78
64	celiprolol	-3.23	-3.64	-0.41
65	NTX-3-propionate (PROP-NTX)	-2.60	-3.73	-1.13
66	benzene	-0.95	-1.76	-0.81
67	corticosterone	-4.22	-3.40	0.82
68	methyl-4-hydroxy benzoate	-2.32	-2.21	0.11
69	betamethasone	-5.70	-3.66	2.04
70	2-cresol (o-cresol)	-1.80	-1.90	-0.10
71	3-cresol (m-cresol)	-1.82	-1.90	-0.08
72	4-cresol (p-cresol)	-1.76	-1.90	-0.14
73	butyl nicotinate	-1.78	-2.30	-0.52
74	ethylaniline	-0.54	-1.94	-1.40
75	o-cresyl glycidyl ether (oCGE)	-4.03	-2.17	1.86
76	nimesulide	-3.00	-3.00	-0.01
77	salicylic acid	-1.89	-1.95	-0.06

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Potts & Guy) (cmh^{-1})	Log K_p (exp)- log K_p (Potts & Guy) (cmh^{-1})
78	N-N-diethyl m-toluamide	-2.65	-2.26	0.39
79	malathion	-0.69	-3.09	-2.40
80	benzyl nicotinate	-1.80	-2.33	-0.53
81	4-bromophenol	-1.44	-2.05	-0.61
82	estriol	-4.40	-2.75	1.65
83	methyl paraben	-2.38	-2.53	-0.15
84	dibutyl squarate	-4.70	-2.34	2.36
85	NTX-3-butyrate (BUT-NTX)	-2.89	-3.47	-0.58
86	NTX-3-valerate (VAL-NTX)	-3.15	-3.55	-0.40
87	triclosan	-4.47	-2.71	1.76
88	4-phenylbutanol	-1.06	-1.80	-0.74
89	propranolol	-2.75	-2.66	0.09
90	3,4 xylenol	-1.44	-2.08	-0.64
91	DEP	-4.94	-2.17	2.77
92	2-naphthol	-1.55	-1.67	-0.12
93	methyl parathion	-4.42	-2.35	2.07
94	androstedione	-2.91	-2.51	0.40
95	n-octanol	-1.21	-1.50	-0.29
96	methiocarb	-2.96	-2.04	0.92
97	NTX-3-hexanoate (HEX-NTX)	-2.92	-3.29	-0.37
98	meperidine	-2.43	-2.06	0.37
99	4-n-butylaniline	-0.39	-1.41	-1.02
100	n-hexyl nicotinate	-1.75	-1.76	-0.01
101	naproxene	-2.54	-1.90	0.64
102	ethanol	-3.50	-0.77	2.73
103	ketoprofen	-3.21	-2.04	1.17
104	cortexolone	-4.12	-2.58	1.54
105	chloroxylenol	-1.23	-1.35	-0.12
106	testosterone	-2.17	-2.14	0.03
107	2-phenylphenol	-1.74	-1.41	0.33
108	butyl paraben	-1.00	-1.42	-0.42
109	thymol	-1.28	-1.12	0.16
110	4-n-pentylaniline	-0.65	-1.15	-0.50
111	sufentanil	-1.92	-2.49	-0.57
112	progesterone	-1.52	-2.01	-0.49
113	parathion	-3.72	-1.83	1.89
114	bisphenol A diglycidyl ether (BADGE)	-6.32	-2.05	4.27
115	diazinon	-2.02	-1.82	0.20
116	pregnenolone	-2.82	-1.87	0.95
117	NTX-3 heptanoate (HEP-NTX)	-3.05	-2.68	0.37
118	b-estradiol	-2.00	-1.54	0.46
119	ibuprofen	-1.44	-1.14	0.30
120	ethinyl estradiol	-4.43	-1.67	2.76
121	dichlofenac	-3.00	-1.65	1.35
122	doxycycline HCL	-5.32	-2.54	2.78
123	fentanyl	-2.25	-1.88	0.37
124	diethyl squarate	-3.92	-0.85	3.07
125	prochloraz	-3.15	-2.07	1.08
126	lindane	-5.23	-1.45	3.78
127	chlorpyrifos	-3.60	-1.53	2.07
128	nonane	-4.38	-0.10	4.28
129	flufenamic acid	-3.26	-0.95	2.31

Compounds 98-129 were eliminated due to high molecular weights and / or unfavourable log P values (MW < 500, -3 < log P < 3). The resulting R^2 increased up to 0.271.

2. Human skin – Predicted permeability using the revised Robinson (1995) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Robinson) (cmh^{-1})	Log K_p (exp)- log K_p (Robinson) (cmh^{-1})
1	aldosterone	-4.24	-3.71	0.53
2	aniline	-1.21	-2.40	-1.19
3	atenolol	-4.30	-4.19	0.11
4	benzene	-0.95	-1.72	-0.77
5	benzoic acid	-2.88	-2.17	0.71
6	benzyl nicotinate	-1.80	-2.51	-0.71
7	bisoprolol	-3.57	-3.42	0.15
8	bisphenol A diglycidyl ether (BADGE)	-6.32	-2.30	4.02
9	4-bromophenol	-1.44	-2.22	-0.78
10	boric acid	-3.30	-2.86	0.44
11	4-n-butylaniline	-0.39	-1.67	-1.28
12	butyl nicotinate	-1.78	-2.44	-0.66
13	butyl paraben	-1.00	-1.75	-0.75
14	2-butoxyethanol	-3.67	-2.92	0.75
15	2-(2-butoxyethoxy)ethanol	-4.45	-3.41	1.04
16	caffeine	-3.68	-3.69	-0.01
17	celiprolol	-3.23	-3.62	-0.39
18	chloroxylenol	-1.23	-1.63	-0.40
19	chlorpyrifos	-3.60	-1.87	1.73
20	codeine	-4.31	-3.62	0.69
21	cortexolone	-4.12	-2.73	1.39
22	corticosterone	-4.22	-3.43	0.79
23	cortisone	-5.00	-3.60	1.40
24	coumarin	-2.04	-2.57	-0.53
25	o-cresyl glycidyl ether (oCGE)	-4.03	-2.31	1.72
26	2-cresol (o-cresol)	-1.80	-1.95	-0.15
27	3-cresol (m-cresol)	-1.82	-1.95	-0.13
28	4-cresol (p-cresol)	-1.76	-1.95	-0.19
29	diazinon	-2.02	-2.11	-0.09
30	dichlofenac	-3.00	-1.98	1.02
31	DEP	-4.94	-2.38	2.56
32	dibutyl squarate	-4.70	-2.53	2.17
33	diethyl squarate	-3.92	-1.30	2.62
34	dimethylformamide	-2.02	-3.40	-1.38
35	2,4 dimethylamine	-3.02	-3.71	-0.69
36	doxycycline HCL	-5.32	-5.08	0.24
37	b-estradiol	-2.00	-1.91	0.09
38	estriol	-4.40	-2.65	1.75
39	estrone	-2.44	-2.19	0.25
40	ethanol	-3.50	-2.62	0.88
41	etodolac	-2.13	-1.99	0.14
42	ethylaniline	-0.54	-2.02	-1.48
43	ethyl nicotinate	-2.22	-2.83	-0.61
44	2-ethoxyethanol	-3.07	-3.27	-0.20
45	2-(2-ethoxyethoxy)ethanol	-3.88	-3.78	0.10
46	2-ethoxyethyl acetate	-3.09	-3.02	0.07
47	famotidine	-4.79	-4.74	0.05
48	fentanyl	-2.25	-2.16	0.09

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Robinson) (cmh^{-1})	Log K_p (exp)- log K_p (Robinson) (cmh^{-1})
49	flufenamic acid	-3.26	-1.46	1.80
50	5-fluorouracil	-4.78	-3.82	0.96
51	griseofulvin	-2.71	-3.50	-0.79
52	1,6-hexanediol diglycidyl ether (HDDGE)	-3.87	-3.51	0.36
53	n-hexyl nicotinate	-1.75	-2.03	-0.28
54	hydrocortisone	-3.80	-3.73	0.07
55	hydromorphone	-4.82	-3.36	1.46
56	hydroquinone	-5.03	-2.57	2.46
57	ibuprofen	-1.44	-1.55	-0.11
58	methyl paraben	-2.38	-2.53	-0.15
59	ITF 296	-2.45	-2.95	-0.50
60	isosorbide dinitrate (ISDN)	-2.35	-3.59	-1.24
61	ketoprofen	-3.21	-2.29	0.92
62	lidocaine	-1.97	-3.05	-1.08
63	lindane	-5.23	-1.82	3.41
64	malathion	-0.69	-3.17	-2.48
65	methanol	-2.80	-2.80	-0.00
66	methotrexate	-3.95	-5.08	-1.13
67	meperidine	-2.43	-2.30	0.13
68	methiocarb	-2.96	-2.27	0.69
69	methyl-4-hydroxy benzoate	-2.32	-2.32	0.00
70	methyl nicotinate	-2.47	-3.02	-0.55
71	methyl parathion	-4.42	-2.55	1.87
72	2-(2-methoxyethoxy)ethanol	-3.69	-3.95	-0.26
73	1-methoxylpropan-2-ol	-3.19	-3.31	-0.12
74	metoprolol	-3.08	-3.21	-0.13
75	morphine	-5.03	-3.87	1.16
76	N-N-diethyl m-toluamide	-2.65	-2.43	0.22
77	naltrexone (NTX)	-2.02	-3.76	-1.74
78	NTX-3-acetate (ACE-NTX)	-2.11	-3.90	-1.79
79	NTX-3-propionate (PROP-NTX)	-2.60	-3.67	-1.07
80	NTX-3-butyrate (BUT-NTX)	-2.89	-3.45	-0.56
81	NTX-3-valerate (VAL-NTX)	-3.15	-3.50	-0.35
82	NTX-3-hexanoate (HEX-NTX)	-2.92	-3.27	-0.35
83	NTX-3 heptanoate (HEP-NTX)	-3.05	-2.74	0.31
84	2-naphthol	-1.55	-1.86	-0.31
85	naproxene	-2.54	-2.16	0.38
86	nicorandil	-4.30	-3.64	0.66
87	nicotinic acid	-4.62	-2.88	1.74
88	nicotine	-1.99	-2.99	-1.00
89	nimesulide	-3.00	-3.11	-0.11
90	3-nitrophenol	-2.25	-2.28	-0.03
91	n-nitrosodiethanolamine	-2.39	-4.10	-1.71
92	nizatidine	-4.43	-4.64	-0.21
93	nonane	-4.38	-0.87	3.51
94	n-octanol	-1.21	-1.69	-0.48
95	oxprenolol	-2.81	-3.12	-0.31
96	parathion	-3.72	-2.12	1.60
97	paraquat	-5.06	-4.96	0.10
98	4-n-pentylaniline	-0.65	-1.50	-0.85
99	phenol	-2.09	-2.15	-0.06
100	2-phenoxyethanol	-2.87	-2.76	0.11

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Robinson) (cmh^{-1})	Log K_p (exp)- log K_p (Robinson) (cmh^{-1})
101	2-phenylethanol	-1.51	-2.35	-0.84
102	4-phenylbutanol	-1.06	-1.98	-0.92
103	2-phenylphenol	-1.74	-1.70	0.04
104	pirimicarb	-2.57	-3.22	-0.65
105	pregnenolone	-2.82	-2.15	0.67
106	prochloraz	-3.15	-2.29	0.86
107	progesterone	-1.52	-2.27	-0.75
108	propranolol	-2.75	-2.81	-0.06
109	propoxur	-3.05	-2.75	0.30
110	ranitidine	-4.05	-4.24	-0.19
111	resorcinol	-3.62	-2.57	1.05
112	salicylic acid	-1.89	-2.08	-0.19
113	squaric acid	-5.12	-3.48	1.64
114	sufentanil	-1.92	-2.64	-0.72
115	testosterone	-2.17	-2.38	-0.21
116	theophylline	-3.36	-3.92	-0.56
117	thymol	-1.28	-1.45	-0.17
118	triclosan	-4.47	-2.86	1.61
119	3,4 xylenol	-1.44	-2.29	-0.85
120	water	-3.15	-2.91	0.24
121	nikel	-3.21	-3.03	0.18
122	adenosine	-3.88	-4.65	-0.78
123	cimetidine	-4.42	-3.89	0.53
124	deoxyadenosine	-3.89	-4.38	-0.49
125	androstedione	-2.91	-2.69	0.22
126	ethinyl estradiol	-4.43	-1.99	2.43
127	prednisone	-4.61	-3.80	0.81
128	prednisolone	-4.63	-3.79	0.84
129	betamethasone	-5.70	-3.62	2.08

Compounds 98-129 were eliminated due to high molecular weights and / or unfavourable log P values (MW < 500, -3 < log P < 3). The resulting R^2 increased up to 0.35.

3. Human skin – Predicted permeability using the Cronin et al. (1999) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp)- log K_p (Cronin) (cmh^{-1})
1	paraquat	-5.06	-7.07	-2.01
2	water	-3.15	-3.58	-0.43
3	doxycycline HCL	-5.32	-7.95	-2.63
4	methotrexate	-3.95	-8.00	-4.05
5	n-nitrosodiethanolamine	-2.39	-4.70	-2.31
6	2-(2-methoxyethoxy)ethanol	-3.69	-4.48	-0.79
7	adenosine	-3.88	-5.89	-2.01
8	dimethylformamide	-2.02	-3.80	-1.78
9	5-fluorouracil	-4.78	-4.29	0.49
10	methanol	-2.80	-3.25	-0.45
11	2-(2-ethoxyethoxy)ethanol	-3.88	-4.24	-0.36
12	famotidine	-4.79	-6.30	-1.51
13	nikel	-3.21	-3.37	-0.16
14	deoxyadenosine	-3.89	-5.34	-1.45
15	1-methoxylpropan-2-ol	-3.19	-3.64	-0.45
16	squaric acid	-5.12	-3.84	1.28

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp)- log K_p (Cronin) (cmh^{-1})
17	nizatidine	-4.43	-6.08	-1.65
18	2-ethoxyethanol	-3.07	-3.58	-0.51
19	theophylline	-3.36	-4.49	-1.13
20	boric acid	-3.30	-3.14	0.16
21	ethanol	-3.50	-2.91	0.59
22	atenolol	-4.30	-5.10	-0.80
23	caffeine	-3.68	-4.21	-0.53
24	2-(2-butoxyethoxy)ethanol	-4.45	-3.78	0.67
25	ranitidine	-4.05	-5.34	-1.29
26	cimetidine	-4.42	-4.62	-0.20
27	nicorandil	-4.30	-4.17	0.13
28	2-butoxyethanol	-3.67	-3.11	0.56
29	2-ethoxyethyl acetate	-3.09	-3.24	-0.15
30	methyl nicotinate	-2.47	-3.25	-0.78
31	nicotinic acid	-4.62	-3.07	1.55
32	morphine	-5.03	-4.71	0.32
33	isosorbide dinitrate (ISDN)	-2.35	-4.18	-1.83
34	2,4 dimethylamine	-3.09	-4.42	-1.33
35	1,6-hexanediol diglycidyl ether (HDDGE)	-3.87	-4.05	-0.18
36	nicotine	-1.99	-3.23	-1.24
37	hydroquinone	-5.03	-2.67	2.36
38	resorcinol	-3.62	-2.67	0.95
39	aniline	-1.21	-2.46	-1.25
40	2-phenoxyethanol	-2.87	-2.91	-0.04
41	ethyl nicotinate	-2.22	-3.02	-0.80
42	codeine	-4.31	-4.43	-0.12
43	naltrexone (NTX)	-2.02	-4.77	-2.75
44	pirimicarb	-2.57	-3.71	-1.14
45	prednisone	-4.61	-4.90	-0.29
46	NTX-3-acetate (ACE-NTX)	-2.11	-5.14	-3.03
47	prednisolone	-4.63	-4.90	-0.27
48	coumarin	-2.04	-2.67	-0.63
49	phenol	-2.09	-2.14	-0.05
50	2-phenylethanol	-1.51	-2.38	-0.87
51	hydromorphone	-4.82	-4.04	0.78
52	hydrocortisone	-3.80	-4.82	-1.02
53	aldosterone	-4.24	-4.79	-0.55
54	lidocaine	-1.97	-3.47	-1.50
55	metoprolol	-3.08	-3.78	-0.70
56	cortisone	-5.00	-4.65	0.35
57	oxprenolol	-2.81	-3.65	-0.84
58	bisoprolol	-3.57	-4.27	-0.70
59	ITF 296	-2.45	-3.36	-0.91
60	benzoic acid	-2.88	-2.15	0.73
61	propoxur	-3.05	-3.02	0.03
62	3-nitrophenol	-2.25	-2.29	-0.04
63	griseofulvin	-2.71	-4.49	-1.78
64	celiprolol	-3.23	-4.75	-1.52
65	NTX-3-propionate (PROP-NTX)	-2.60	-4.91	-2.31
66	benzene	-0.95	-1.60	-0.65
67	corticosterone	-4.22	-4.37	-0.15
68	methyl-4-hydroxy benzoate	-2.32	-2.36	-0.04

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp)- log K_p (Cronin) (cmh^{-1})
69	betamethasone	-5.70	-4.82	0.88
70	2-cresol (o-cresol)	-1.80	-1.86	-0.06
71	3-cresol (m-cresol)	-1.82	-1.86	-0.04
72	4-cresol (p-cresol)	-1.76	-1.86	-0.10
73	butyl nicotinate	-1.78	-2.55	-0.77
74	ethylaniline	-0.54	-1.95	-1.41
75	o-cresyl glycidyl ether (oCGE)	-4.03	-2.36	1.67
76	nimesulide	-3.00	-3.80	-0.80
77	salicylic acid	-1.89	-2.03	-0.14
78	N-N-diethyl m-toluamide	-2.65	-2.56	0.09
79	malathion	-0.69	-3.97	-3.28
80	benzyl nicotinate	-1.80	-2.72	-0.92
81	4-bromophenol	-1.44	-2.26	-0.82
82	methyl paraben	-2.38	-2.53	-0.15
83	dibutyl squarate	-4.70	-2.77	1.93
84	NTX-3-butyrate (BUT-NTX)	-2.89	-4.68	-1.79
85	NTX-3-valerate (VAL-NTX)	-3.15	-4.82	-1.67
86	triclosan	-4.47	-3.41	1.06
87	4-phenylbutanol	-1.06	-1.91	-0.85
88	propranolol	-2.75	-3.37	-0.62
89	3,4 xylenol	-1.44	-2.41	-0.97
90	DEP	-4.94	-2.58	2.36
91	2-naphthol	-1.55	-1.74	-0.19
92	methyl parathion	-4.42	-2.92	1.50
93	androstedione	-2.91	-3.18	-0.28
94	estriol	-4.40	-3.14	1.26
95	n-octanol	-1.21	-1.51	-0.30
96	methiocarb	-2.96	-2.44	0.52
97	NTX-3-hexanoate (HEX-NTX)	-2.92	-4.59	-1.67
98	meperidine	-2.43	-2.55	-0.12
99	4-n-butylaniline	-0.39	-1.48	-1.09
100	n-hexyl nicotinate	-1.75	-2.08	-0.33
101	naproxene	-2.54	-2.32	0.22
102	ketoprofen	-3.21	-2.55	0.66
103	cortexolone	-4.12	-3.47	0.65
104	chloroxylenol	-1.23	-1.44	-0.21
105	testosterone	-2.17	-2.78	-0.61
106	2-phenylphenol	-1.74	-1.56	0.18
107	estrone	-2.44	-2.47	-0.03
108	butyl paraben	-1.00	-1.66	-0.66
109	thymol	-1.28	-1.17	0.11
110	4-n-pentylaniline	-0.65	-1.25	-0.60
111	sufentanil	-1.92	-3.52	-1.60
112	progesterone	-1.52	-2.74	-1.22
113	parathion	-3.72	-2.46	1.26
114	bisphenol A diglycidyl ether (BADGE)	-6.32	-2.88	3.44
115	diazinon	-2.02	-2.49	-0.47
116	pregnenolone	-2.82	-2.59	0.23
117	NTX-3 heptanoate (HEP-NTX)	-3.05	-3.98	-0.93
118	etodolac	-2.13	-2.26	-0.13
119	b-estradiol	-2.00	-2.10	-0.10
120	ibuprofen	-1.44	-1.40	0.04

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp)- log K_p (Cronin) (cmh^{-1})
121	ethinyl estradiol	-4.43	-2.30	2.12
122	dichlofenac	-3.00	-2.29	0.71
123	fentanyl	-2.25	-2.68	-0.43
124	diethyl squarate	-3.92	-0.95	2.97
125	prochloraz	-3.15	-3.03	0.12
126	lindane	-5.23	-2.05	3.18
127	chlorpyrifos	-3.60	-2.35	1.25
128	nonane	-4.38	0.01	4.39
129	flufenamic acid	-3.26	-1.47	1.79

The following compounds were eliminated from all datasets:

- Compounds 98-129 were eliminated due to high molecular weights and / or unfavourable log P values (MW < 500, -3 < log P < 3). The resulting R^2 increased up to 0.26.
- A further reduction occurred from a total of 97 compounds down to 59 due to residual values being less than 1 log unit. The resulting R^2 increased up to 0.80.

4. Human skin – Predicted permeability using the revised Brown and Rossi (1995) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp)- log K_p (Brown & Rossi) (cmh^{-1})
1	paraquat	-5.06	-4.11	0.95
2	erioglaucine	-5.87	-3.20	2.67
3	water	-3.15	-3.11	0.04
4	doxycycline HCL	-5.32	-3.10	2.22
5	methotrexate	-3.95	-3.04	0.91
6	n-nitrosodiethanolamine	-2.39	-3.04	-0.65
7	2-(2-methoxyethoxy)ethanol	-3.69	-2.96	0.73
8	adenosine	-3.88	-2.87	1.01
9	dimethylformamide	-2.02	-2.78	-0.76
10	5-fluorouracil	-4.78	-2.69	2.09
11	methanol	-2.80	-2.66	0.14
12	2-(2-ethoxyethoxy)ethanol	-3.88	-2.60	1.28
13	famotidine	-4.79	-2.56	2.23
14	nikel	-3.21	-2.51	0.71
15	deoxyadenosine	-3.89	-2.49	1.40
16	1-methoxylpropan-2-ol	-3.19	-2.45	0.74
17	squaric acid	-5.12	-2.41	2.71
18	nizatidine	-4.43	-2.40	2.03
19	2-ethoxyethanol	-3.07	-2.40	0.67
20	theophylline	-3.36	-2.37	0.99
21	boric acid	-3.30	-2.25	1.05
22	ethanol	-3.50	-2.19	1.31
23	atenolol	-4.30	-2.11	2.19
24	caffeine	-3.68	-1.96	1.72
25	2-(2-butoxyethoxy)ethanol	-4.45	-1.87	2.58
26	ranitidine	-4.05	-1.87	2.18
27	cimetidine	-4.42	-1.79	2.63
28	nicorandil	-4.30	-1.76	2.54
29	2-butoxyethanol	-3.67	-1.66	2.01
30	2-ethoxyethyl acetate	-3.09	-1.65	1.44
31	methyl nicotinate	-2.47	-1.61	0.86
32	nicotinic acid	-4.62	-1.57	3.05

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp)- log K_p (Brown & Rossi) (cmh^{-1})
33	morphine	-5.03	-1.55	3.48
34	isosorbide dinitrate (ISDN)	-2.35	-1.52	0.83
35	2,4 dimethylamine	-3.09	-1.46	1.63
36	1,6-hexanediol diglycidyl ether (HDDGE)	-3.87	-1.46	2.41
37	nicotine	-1.99	-1.35	0.64
38	hydroquinone	-5.03	-1.33	3.70
39	resorcinol	-3.62	-1.33	2.29
40	aniline	-1.21	-1.29	-0.08
41	2-phenoxyethanol	-2.87	-1.28	1.59
42	ethyl nicotinate	-2.22	-1.26	0.96
43	codeine	-4.31	-1.15	3.16
44	naltrexone (NTX)	-2.02	-1.07	0.95
45	pirimicarb	-2.57	-1.07	1.50
46	prednisone	-4.61	-1.03	3.58
47	NTX-3-acetate (ACE-NTX)	-2.11	-1.02	1.09
48	prednisolone	-4.63	-1.01	3.62
49	coumarin	-2.04	-0.99	1.05
50	phenol	-2.09	-0.99	1.10
51	2-phenylethanol	-1.51	-0.95	0.56
52	hydromorphone	-4.82	-0.93	3.89
53	hydrocortisone	-3.80	-0.93	2.87
54	aldosterone	-4.24	-0.91	3.33
55	lidocaine	-1.97	-0.89	1.08
56	metoprolol	-3.08	-0.87	2.21
57	cortisone	-5.00	-0.80	4.20
58	oxprenolol	-2.81	-0.78	2.03
59	bisoprolol	-3.57	-0.78	2.79
60	ITF 296	-2.45	-0.77	1.68
61	benzoic acid	-2.88	-0.76	2.12
62	propoxur	-3.05	-0.74	2.31
63	3-nitrophenol	-2.25	-0.74	1.51
64	griseofulvin	-2.71	-0.73	1.98
65	celiprolol	-3.23	-0.72	2.51
66	NTX-3-propionate (PROP-NTX)	-2.60	-0.70	1.90
67	benzene	-0.95	-0.69	0.26
68	corticosterone	-4.22	-0.69	3.53
69	methyl-4-hydroxy benzoate	-2.32	-0.68	1.64
70	betamethasone	-5.70	-0.67	5.03
71	2-cresol (o-cresol)	-1.80	-0.65	1.15
72	3-cresol (m-cresol)	-1.82	-0.65	1.17
73	4-cresol (p-cresol)	-1.76	-0.65	1.11
74	butyl nicotinate	-1.78	-0.62	1.16
75	ethylaniline	-0.54	-0.62	-0.08
76	o-cresyl glycidyl ether (oCGE)	-4.03	-0.59	3.44
77	nimesulide	-3.00	-0.56	2.44
78	salicylic acid	-1.89	-0.54	1.35
79	N-N-diethyl m-toluamide	-2.65	-0.53	2.12
80	malathion	-0.69	-0.52	0.17
81	benzyl nicotinate	-1.80	-0.49	1.31
82	4-bromophenol	-1.44	-0.46	0.98
83	methyl paraben	-2.38	-2.53	-0.15
84	dibutyl squarate	-4.70	-0.44	4.26

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp)- log K_p (Brown & Rossi) (cmh^{-1})
85	NTX-3-butyrate (BUT-NTX)	-2.89	-0.44	2.45
86	NTX-3-valerate (VAL-NTX)	-3.15	-0.44	2.71
87	triclosan	-4.47	-0.43	4.04
88	4-phenylbutanol	-1.06	-0.39	0.67
89	propranolol	-2.75	-0.37	2.38
90	3,4 xylenol	-1.44	-0.37	1.07
91	DEP	-4.94	-0.35	4.59
92	2-naphthol	-1.55	-0.33	1.22
93	methyl parathion	-4.42	-0.31	4.11
94	androstedione	-2.91	-0.31	2.60
95	estriol	-4.40	-0.29	4.11
96	n-octanol	-1.21	-0.29	0.92
97	methiocarb	-2.96	-0.27	2.69
98	NTX-3-hexanoate (HEX-NTX)	-2.92	-0.24	2.68
99	meperidine	-2.43	-0.22	2.21
100	4-n-butylaniline	-0.39	-0.20	0.19
101	n-hexyl nicotinate	-1.75	-0.20	1.55
102	naproxene	-2.54	-0.20	2.34
103	ketoprofen	-3.21	-0.19	3.02
104	cortexolone	-4.12	-0.18	3.94
105	chloroxylenol	-1.23	-0.16	1.07
106	testosterone	-2.17	-0.15	2.02
107	2-phenylphenol	-1.74	-0.15	1.59
108	estrone	-2.44	-0.12	2.32
109	butyl paraben	-1.00	-0.11	0.89
110	thymol	-1.28	-0.11	1.17
111	4-n-pentylaniline	-0.65	-0.09	0.56
112	sufentanil	-1.92	-0.09	1.83
113	progesterone	-1.52	-0.08	1.44
114	parathion	-3.72	-0.08	3.64
115	bisphenol A diglycidyl ether (BADGE)	-6.32	-0.06	6.26
116	diazinon	-2.02	-0.06	1.96
117	pregnenolone	-2.82	-0.06	2.76
118	NTX-3 heptanoate (HEP-NTX)	-3.05	-0.06	2.99
119	etodolac	-2.13	-0.06	2.07
120	b-estradiol	-2.00	-0.05	1.95
121	ibuprofen	-1.44	-0.05	1.39
122	ethinyl estradiol	-4.43	-0.05	4.38
123	dichlofenac	-3.00	-0.05	2.95
124	fentanyl	-2.25	-0.05	2.20
125	diethyl squarate	-3.92	-0.04	3.88
126	prochloraz	-3.15	-0.04	3.11
127	lindane	-5.23	-0.03	5.20
128	chlorpyrifos	-3.60	-0.02	3.58
129	nonane	-4.38	-0.01	4.37
130	flufenamic acid	-3.26	-0.01	3.25

The following compounds were eliminated from all datasets:

- Compounds 98-129 were eliminated due to high molecular weights and / or unfavourable log P values (MW < 500, -3 < log P <3).
- An additional compound was inserted in the database. It was not recorded before due to difficulties in obtaining MW. The resulting R^2 increased up to 0.159.

5. Human skin – Predicted permeability using the Barratt (1995b) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Barratt) (cmh^{-1})	Log K_p (exp)- log K_p (Barratt) (cmh^{-1})
1	paraquat	-5.06	-18.67	-13.61
2	water	-3.15	-3.66	-0.51
3	doxycycline HCL	-5.32	-41.38	-36.06
4	methotrexate	-3.95	-15.24	-11.29
5	n-nitrosodiethanolamine	-2.39	-7.84	-5.45
6	2-(2-methoxyethoxy)ethanol	-3.69	-1.71	1.98
7	adenosine	-3.88	-14.83	-10.96
8	dimethylformamide	-2.02	-1.42	0.60
9	methanol	-2.80	0.53	3.33
10	2-(2-ethoxyethoxy)ethanol	-3.88	-1.21	2.67
11	famotidine	-4.79	-12.40	-7.61
12	nikel	-3.21	-60.04	-56.83
13	deoxyadenosine	-3.89	-12.44	-8.55
14	1-methoxylpropan-2-ol	-3.19	1.94	5.13
15	squaric acid	-5.12	-15.21	-10.09
16	nizatidine	-4.43	-10.87	-6.44
17	2-ethoxyethanol	-3.07	-0.03	3.04
18	theophylline	-3.36	-15.00	-11.64
19	boric acid	-3.30	-9.78	-6.48
20	ethanol	-3.50	1.55	5.05
21	atenolol	-4.30	-10.59	-6.29
22	caffeine	-3.68	-13.32	-9.64
23	2-(2-butoxyethoxy)ethanol	-4.45	-0.98	3.47
24	ranitidine	-4.05	-10.23	-6.18
25	cimetidine	-4.42	-9.92	-5.50
26	nicorandil	-4.30	-7.58	-3.28
27	2-butoxyethanol	-3.67	-0.26	3.41
28	2-ethoxyethyl acetate	-3.09	-0.70	2.39
29	methyl nicotinate	-2.47	-4.77	-2.30
30	nicotinic acid	-4.62	-12.17	-7.55
31	morphine	-5.03	-14.37	-9.34
32	isosorbide dinitrate (ISDN)	-2.35	-6.66	-4.31
33	2,4 dimethylamine	-3.02	-7.50	-4.48
34	1,6-hexanediol diglycidyl ether (HDDGE)	-3.87	-7.12	-3.25
35	nicotine	-1.99	-2.74	-0.75
36	hydroquinone	-5.03	-9.17	-4.14
37	resorcinol	-3.62	-6.83	-3.21
38	aniline	-1.21	-2.10	-0.89
39	2-phenoxyethanol	-2.87	-3.29	-0.42
40	ethyl nicotinate	-2.22	-2.51	-0.29
41	codeine	-4.31	-10.14	-5.83
42	naltrexone (NTX)	-2.02	-10.87	-8.85
43	pirimicarb	-2.57	-13.36	-10.79
44	prednisone	-4.61	-23.70	-19.09
45	NTX-3-acetate (ACE-NTX)	-2.11	-9.16	-7.05
46	prednisolone	-4.63	-23.24	-18.61
47	coumarin	-2.04	-5.23	-3.19
48	phenol	-2.09	-3.59	-1.50
49	2-phenylethanol	-1.51	-1.16	0.35
50	hydromorphone	-4.82	-14.08	-9.26
51	5-fluorouracil	-4.78	-13.21	-8.43

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Barratt) (cmh^{-1})	Log K_p (exp)- log K_p (Barratt) (cmh^{-1})
52	hydrocortisone	-3.80	-12.99	-9.19
53	aldosterone	-4.24	-10.77	-6.53
54	lidocaine	-1.97	-5.79	-3.82
55	metoprolol	-3.08	-8.30	-5.22
56	cortisone	-5.00	-12.81	-7.81
57	oxprenolol	-2.81	-7.62	-4.81
58	bisoprolol	-3.57	-7.78	-4.21
59	ITF 296	-2.45	-5.22	-2.77
60	benzoic acid	-2.88	-6.74	-3.86
61	propoxur	-3.05	-6.14	-3.09
62	3-nitrophenol	-2.25	-5.91	-3.66
63	griseofulvin	-2.71	-12.65	-9.94
64	celiprolol	-3.23	-8.64	-5.41
65	NTX-3-propionate (PROP-NTX)	-2.60	-10.18	-7.58
66	benzene	-0.95	-1.67	-0.72
67	corticosterone	-4.22	-11.09	-6.87
68	methyl-4-hydroxy benzoate	-2.32	-7.24	-4.92
69	betamethasone	-5.70	-24.33	-18.63
70	2-cresol (o-cresol)	-1.80	-2.88	-1.08
71	3-cresol (m-cresol)	-1.82	-2.13	-0.31
72	4-cresol (p-cresol)	-1.76	-2.96	-1.20
73	butyl nicotinate	-1.78	-5.01	-3.23
74	ethylaniline	-0.54	0.74	1.28
75	o-cresyl glycidyl ether (oCGE)	-4.03	-3.30	0.73
76	nimesulide	-3.00	-8.98	-5.99
77	salicylic acid	-1.89	-7.97	0.00
78	N-N-diethyl m-toluamide	-2.65	-0.53	2.12
79	malathion	-0.69	-3.67	-2.98
80	benzyl nicotinate	-1.80	-3.35	-1.55
81	4-bromophenol	-1.44	-4.59	-3.15
82	methyl paraben	-2.38	-2.53	-0.15
83	dibutyl squarate	-4.70	-9.35	-4.65
84	NTX-3-butyrate (BUT-NTX)	-2.89	-8.31	-5.42
85	NTX-3-valerate (VAL-NTX)	-3.15	-7.54	-4.39
86	triclosan	-4.47	-13.39	-8.92
87	4-phenylbutanol	-1.06	-2.30	-1.24
88	propranolol	-2.75	-9.45	-6.70
89	3,4 xylenol	-1.44	-4.54	-3.10
90	DEP	-4.94	-2.14	2.80
91	2-naphthol	-1.55	-6.29	-4.74
92	methyl parathion	-4.42	-3.94	0.48
93	androstedione	-2.91	-12.93	-10.02
94	estriol	-4.40	-13.74	-9.34
95	n-octanol	-1.21	-0.66	0.55
96	methiocarb	-2.96	-6.74	-3.78
97	NTX-3-hexanoate (HEX-NTX)	-2.92	-6.45	-3.53
98	meperidine	-2.43	-12.71	-10.28
99	4-n-butylaniline	-0.39	-0.66	-0.27
100	naproxene	-2.54	-7.93	-5.39
101	ketoprofen	-3.21	-5.83	-2.62
102	cortexolone	-4.12	-11.11	-6.99
103	chloroxylenol	-1.23	-5.64	-4.41

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Barratt) (cmh^{-1})	Log K_p (exp)- log K_p (Barratt) (cmh^{-1})
104	testosterone	-2.17	-8.41	-6.24
105	2-phenylphenol	-1.74	-5.78	-4.04
106	estrone	-2.44	-11.99	-9.55
107	butyl paraben	-1.00	-3.99	-2.99
108	thymol	-1.28	-2.78	-1.50
109	sufentanil	-1.92	-6.77	-4.85
110	progesterone	-1.52	-6.99	-5.47
111	parathion	-3.72	-2.25	1.47
112	bisphenol A diglycidyl ether (BADGE)	-6.32	-2.77	3.55
113	diazinon	-2.02	-5.46	-3.44
114	pregnenolone	-2.82	-9.60	-6.78
115	NTX-3 heptanoate (HEP-NTX)	-3.05	-5.62	-2.57
116	etodolac	-2.13	-7.52	-5.39
117	b-estradiol	-2.00	-8.41	-6.41
118	ibuprofen	-1.44	-3.99	-2.55
119	ethinyl estradiol	-4.43	-12.95	-8.52
120	dichlofenac	-3.00	-14.98	-11.98
121	fentanyl	-2.25	-5.44	-3.19
122	diethyl squarate	-3.92	-5.74	-1.82
123	prochloraz	-3.15	-4.35	-1.20
124	lindane	-5.23	-5.96	-0.73
125	chlorpyrifos	-3.60	-3.44	0.16
126	nonane	-4.38	2.44	6.82
127	flufenamic acid	-3.26	-6.16	-2.90

The following compounds were eliminated from all datasets:

- Compounds 98-129 were eliminated due to high MW and / or unfavourable log P values (MW < 500, -3 < log P < 3).
- Compounds 101 and 111 were also eliminated form the dataset. The regression coefficient was 0.21.
- A further reduction occurred from a total of 97 compounds down to 512 due to residual values being less than 1 log unit.

Figure 1. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Potts and Guy (n = 129).

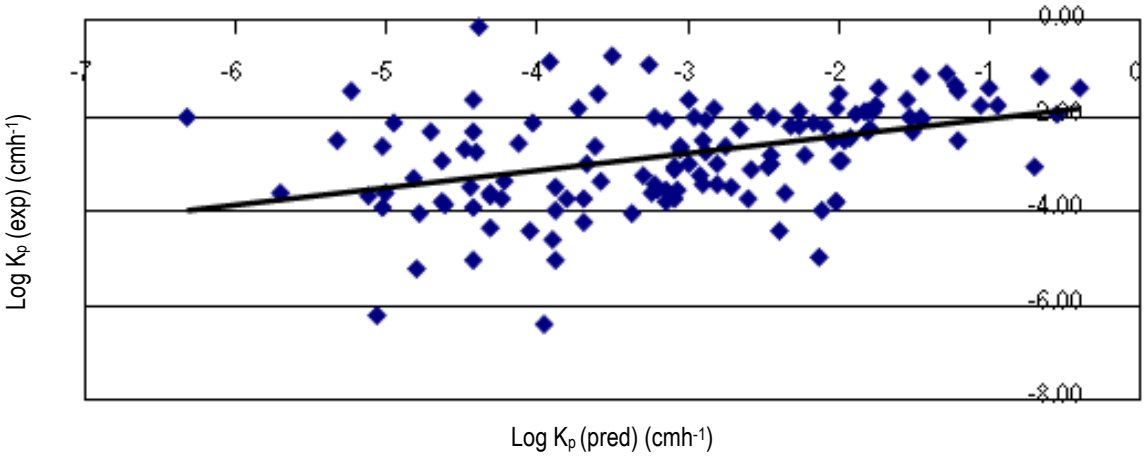


Figure 2. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Potts and Guy (n=97).

R^2= 0.2708

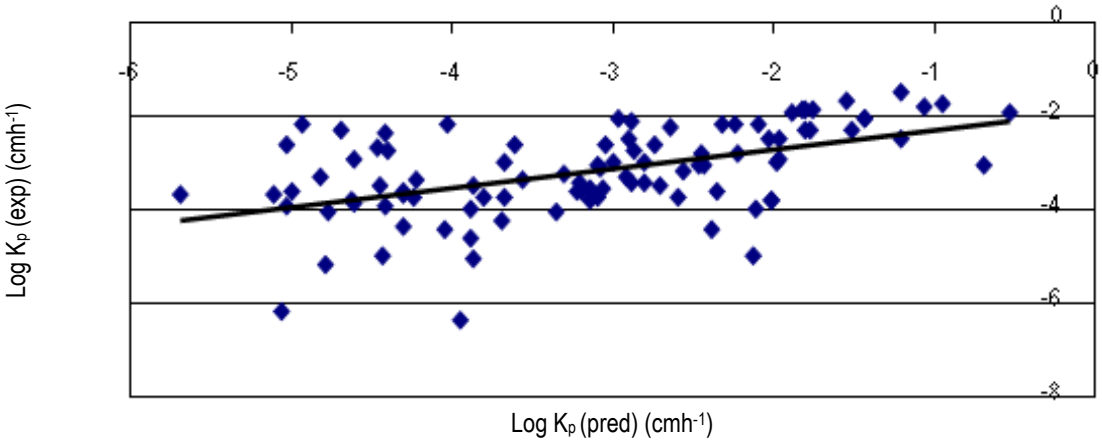


Figure 3. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Robinson (n=129).

R^2 = 0.2514

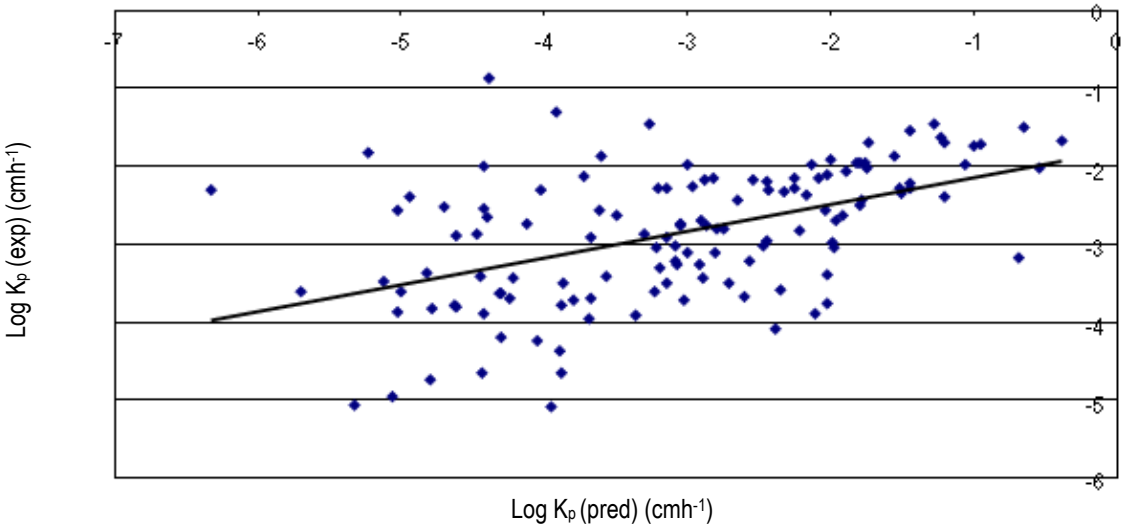


Figure 4. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Robinson (n=97).

R^2 = 0.3483

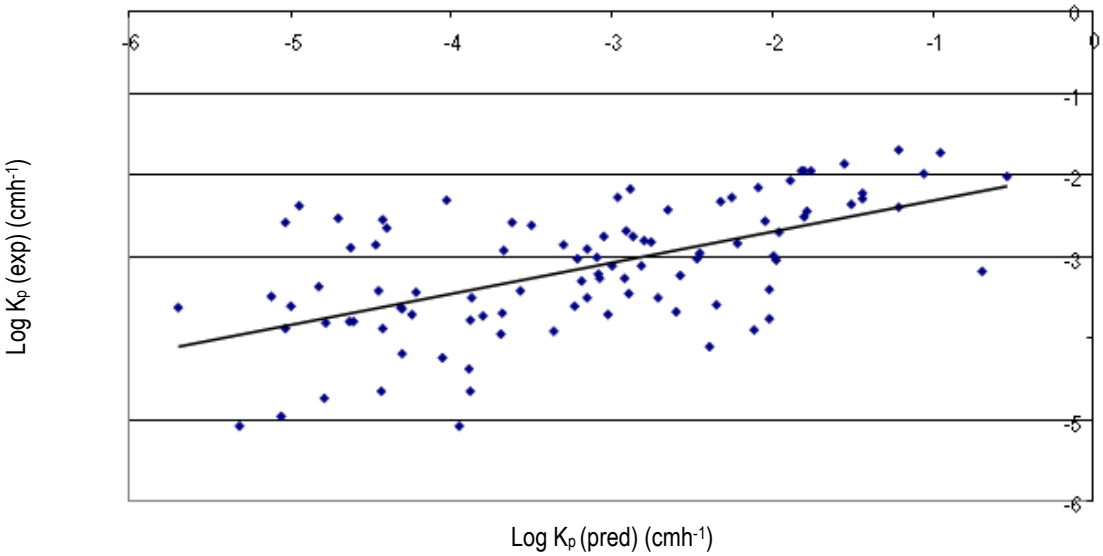


Figure 5. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Cronin (n=129).

$R^2 = 0.2569$

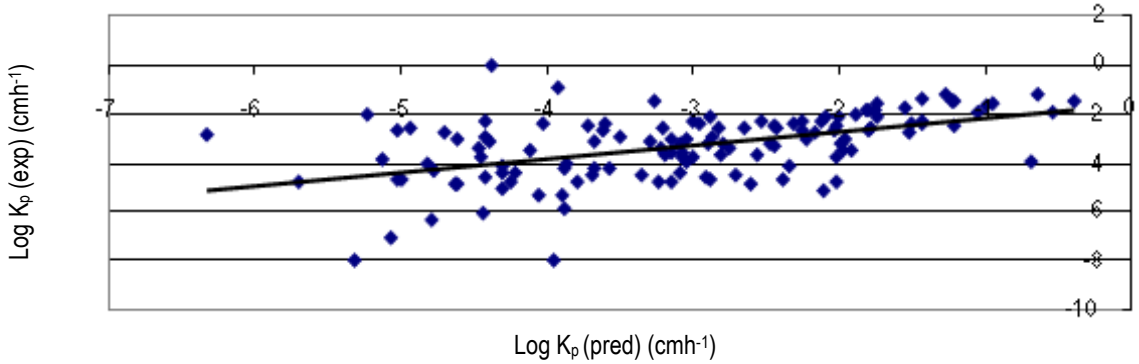


Figure 6. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Cronin (n=97).

$R^2 = 0.3261$

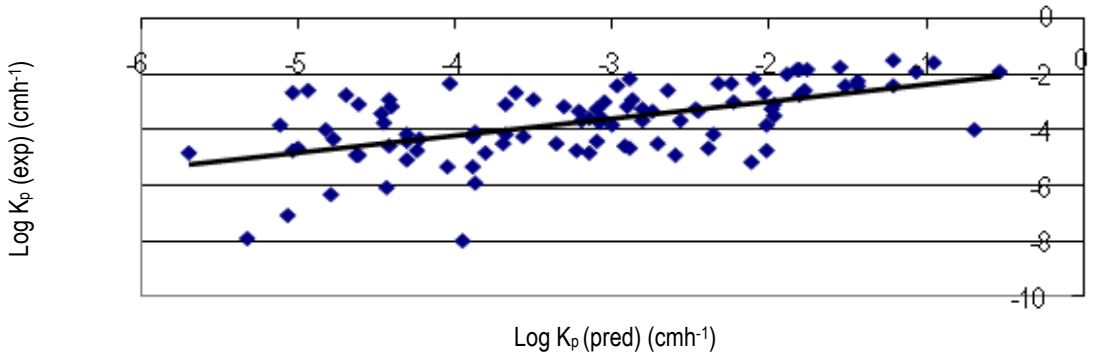


Figure 7. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Brown and Rossi (n=130).

$R^2 = 0.1389$

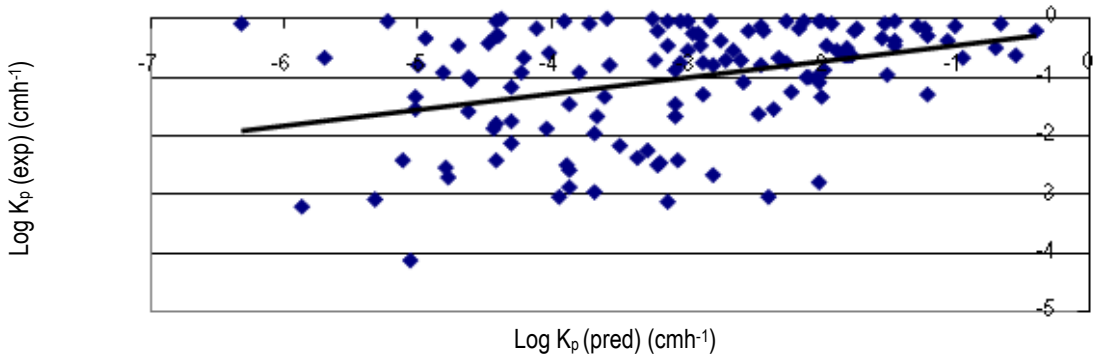


Figure 8. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Brown and Rossi (n=98).

$R^2 = 0.1594$

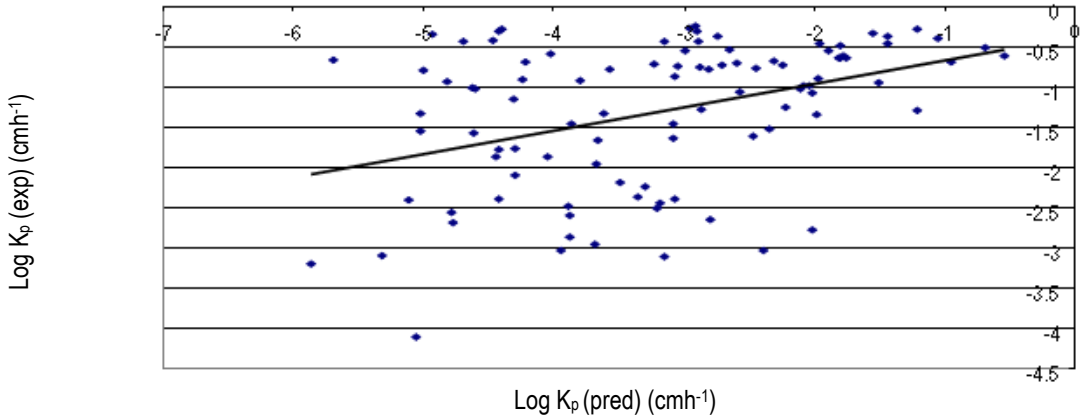


Figure 9. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Barratt (n=127).

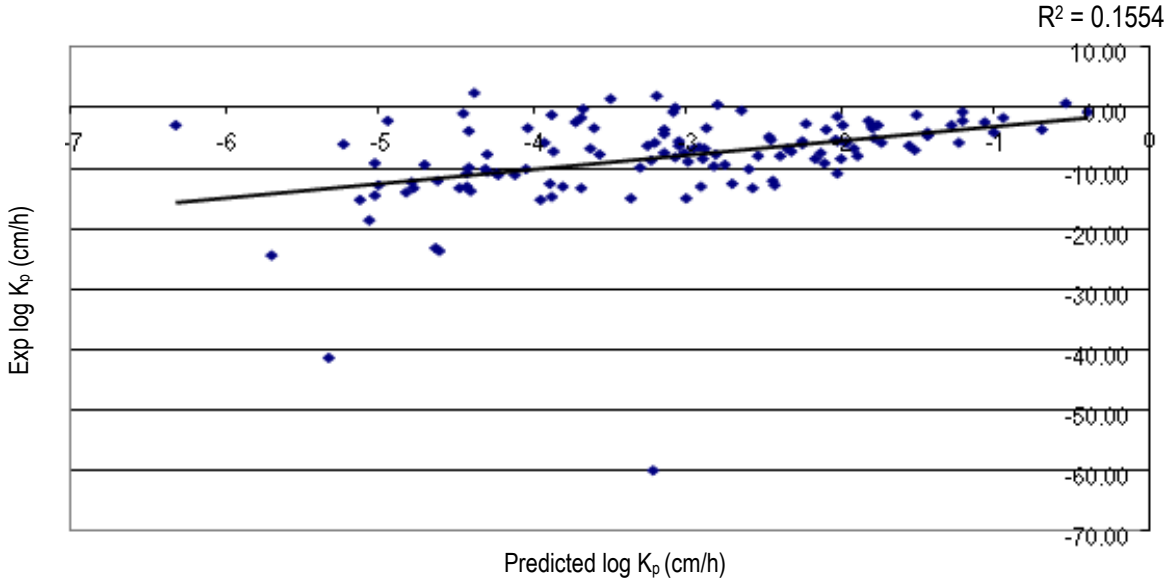
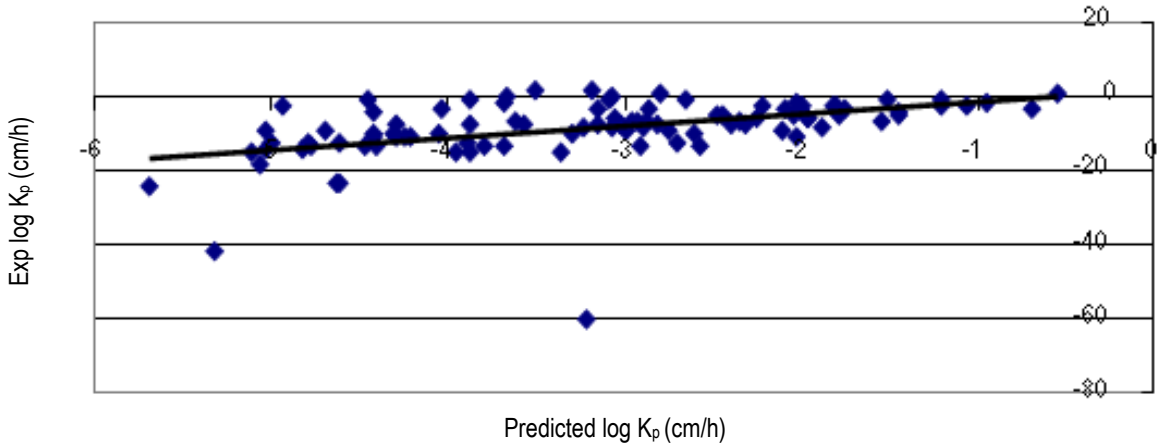


Figure 10. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Barratt (n=97).



Appendix 16. Database C. Mouse skin dataset – Experimental vs predicted K_p values

Mouse skin dataset – Experimental permeability coefficients and drug properties

No	Name	MW	MPt (°C)	Log P KOWWIN	Log K_p (cmh^{-1})	Journal
1	urea	60.6	135.00	-1.56	-3.15	*S. African J.Sci*. 84, 440-441
2	water	18.02	0.00	-1.38	-2.92	*J.Investig.Dermatol*. 75, 346-352
3	thiourea	76.12	176.00	-1.31	-4.02	*Int.J.Pharm*.36, 61-66
4	5-fluorouracil	130.01	281.00	-0.81	-4.22	*J.Investig.Pharmacol*. 94, 235-240
5	methanol	32.04	-98.00	-0.63	-2.74	*J.Investig.Dermatol*. 75, 346-352
6	squaric acid	114.06	293.00	-0.44	-3.15	*Arch.Dermatol.Res*. 280, 57-60
7	ethanol	46.07	-114.10	-0.14	-2.72	*J.Invest.Dermatol*. 75, 346-352
8	atenolol	266.30	147.00	-0.03	-1.52	*Ind.J.Exp.Biol*. 31, 691-693
9	caffeine	194.20	238.00	0.16	-3.59	*J.Cont.Release*. 33, 71-77
10	nicorandil	211.18	92.50	0.43	-3.00	*J.Pharm.Sci*. 80, 104-107
11	morphine	285.30	255.00	0.72	-3.82	*Int.J.Pharm*. 299, 131-137
12	propranolol HCL	295.00	233.20	0.74	-4.30	*J.Pharm.Sci*. 86, 1369-1372
13	n-butanol	74.14	-89.80	0.84	-1.94	*J.Invest.Dermatol*. 75, 346-352
14	1,6-hexanediol diglycidyl ether (HDDGE)	230.20	84.83	0.84	-3.24	*Xenobiotica* 30, 469-483
15	coumarin	146.15	70.60	1.51	-3.00	*Toxicol.Appl.Pharmacol*.145, 34-42
16	hydrocortisone	362.50	220.00	1.62	-4.00	*J.Pharm.Sci*. 73, 1287-1290
17	lidocaine	234.34	67.00	1.66	-2.05	*Int.J.Pharm*. 71, 167-173
18	n-heptanol	116.20	-34.00	1.82	-0.99	*J.Investig.Dermatol*. 75, 346-352
19	corticosterone	346.50	183.00	1.99	-3.28	*J.Pharm.Sci*. 76, 123-126
20	n-hexanol	102.18	-52.00	2.03	-1.43	*J.Investig.Dermatol*. 75, 346-352
21	o-cresyl glycidyl ether (oCGE)	164.20	34.98	2.16	-3.75	*Xenobiotica* 30, 469-483
22	salicylic acid	138.10	158.00	2.24	-1.93	*J.Pharm.Pharmacol*. 45, 414-418
23	N-N-diethyl m-toluamide	191.28	-45.00	2.26	-2.46	*Toxicol.Vitro* 7, 167-176
24	dibutyl squarate	226.27	176.71	2.45	-3.07	*Arch.Dermatol.Res*. 280, 57-60
25	n-octanol	130.23	-15.50	2.81	-1.01	*J.Investig.Dermatol*. 75, 346-352
26	atrazine	215.69	175.00	2.82	-3.11	*Toxicol.Sci*. 68, 18-23
27	etorphine	411.55	215.00	3.02	-2.34	*Pharmaceut.Res*. 9, 963-965
28	17a-hydroxyprogesterone	330.50	276.00	3.08	-3.06	*J.Pharm.Sci*. 76, 123-126
29	deoxycortisone	330.47	141.50	3.12	-2.47	*J.Pharm.Sci*. 76, 123-126
30	alachlor	269.77	40.00	3.37	-3.18	*Toxicol.Sci*. 68, 18-23
31	TDCPP	430.91	27.00	3.65	-3.25	*Food Chem.Toxicol*. 39, 1263-1270
32	progesterone	314.50	121.00	3.67	-1.96	*J.Pharm.Sci*. 76, 123-126
33	bisphenol A diglycidyl ether (BADGE)	340.80	10.00	3.84	-5.07	*Xenobiotica* 30, 469-483
34	diethyl squarate	170.16	131.55	4.07	-3.00	*Arch.Dermatol.Res*. 280, 57-60
35	prednisolone 21-heptanoate	472.62	186.00	4.60	-4.11	*Int.J.Pharm*. 158, 11-18

Predicted permeability coefficient(s) for mouse skin using different models

1. Mouse skin – Predicted permeability using the Potts and Guy (1992) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Potts & Guy) (cmh^{-1})	Log K_p (exp)- log K_p (Potts & Guy) (cmh^{-1})
1	urea	-3.15	-4.18	-1.03
2	water	-2.92	-3.79	-0.87
3	thiourea	-4.02	-4.09	-0.07
4	5-fluorouracil	-4.22	-4.07	0.15
5	methanol	-2.74	-3.34	-0.60
6	squaric acid	-3.15	-3.71	-0.56
7	ethanol	-2.72	-3.08	-0.36
8	atenolol	-1.52	-4.35	-2.83
9	caffeine	-3.59	-3.77	-0.18
10	nicorandil	-3.00	-3.68	-0.68

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Potts & Guy) (cmh^{-1})	Log K_p (exp)- log K_p (Potts & Guy) (cmh^{-1})
11	morphine	-3.82	-3.93	-0.11
12	propranolol HCL	-4.30	-3.98	0.32
13	n-butanol	-1.94	-2.56	-0.62
14	1,6-hexanediol diglycidyl ether (HDDGE)	-3.24	-3.51	-0.27
15	coumarin	-3.00	-2.52	0.48
16	hydrocortisone	-4.00	-3.76	0.24
17	lidocaine	-2.05	-2.95	-0.90
18	n-heptanol	-0.99	-2.12	-1.13
19	corticosterone	-3.28	-3.40	-0.12
20	n-hexanol	-1.43	-1.88	-0.45
21	o-cresyl glycidyl ether (oCGE)	-3.75	-2.17	1.58
22	salicylic acid	-1.93	-1.95	-0.02
23	N-N-diethyl m-toluamide	-2.46	-2.26	0.20
24	dibutyl squarate	-3.07	-2.34	0.73
25	n-octanol	-1.01	-1.50	-0.49
26	atrazine	-3.11	-2.01	1.10
27	etorphine	-2.34	-3.07	-0.73
28	17a-hydroxyprogesterone	-3.06	-2.53	0.53
29	deoxycortisone	-2.47	-2.50	-0.03
30	alachlor	-3.18	-1.95	1.23
31	TDCPP	-3.25	-2.74	0.51
32	progesterone	-1.96	-2.01	-0.05
33	bisphenol A diglycidyl ether (BADGE)	-5.07	-2.05	3.02
34	diethyl squarate	-3.00	-0.85	2.15
35	prednisolone 21-heptanoate	-4.11	-2.32	1.79

2. Mouse skin – Predicted permeability using the revised Brown and Rossi (1995) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp)- log K_p (Brown & Rossi) (cmh^{-1})
1	alachlor	-3.18	-0.13	3.05
2	atenolol	-1.52	-2.11	-0.59
3	atrazine	-3.11	-0.28	2.83
4	bisphenol A diglycidyl ether (BADGE)	-5.07	-0.06	5.01
5	n-butanol	-1.94	-1.46	0.48
6	caffeine	-3.59	-1.96	1.63
7	corticosterone	-3.28	-0.69	2.59
8	coumarin	-3.00	-0.99	2.01
9	o-cresyl glycidyl ether (oCGE)	-3.75	-0.59	3.16
10	deoxycortisone	-2.47	-0.19	2.28
11	dibutyl squarate	-3.07	-0.44	2.63
12	diethyl squarate	-3.00	-0.04	2.96
13	ethanol	-2.72	-2.19	0.53
14	etorphine	-2.34	-0.22	2.12
15	5-fluorouracil	-4.22	-2.69	1.53
16	n-hexanol	-1.43	-0.66	0.77
17	1,6-hexanediol diglycidyl ether (HDDGE)	-3.24	-1.46	1.78
18	n-heptanol	-0.99	-0.79	0.20
19	hydrocortisone	-4.00	-0.92	3.08
20	17a-hydroxyprogesterone	-3.06	-0.20	2.86
21	lidocaine	-2.05	-0.89	1.16
22	N-N-diethyl m-toluamide	-2.46	-0.53	1.93
23	methanol	-2.74	-2.55	0.19

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp)- log K_p (Brown & Rossi) (cmh^{-1})
24	morphine	-3.82	-1.55	2.27
25	nicorandil	-3.00	-1.76	1.24
26	n-octanol	-1.01	-0.29	0.72
27	prednisolone 21-heptanoate	-4.11	-0.02	4.09
28	progesterone	-1.96	-0.08	1.88
29	propranolol HCL	-4.30	-1.54	2.76
30	salicylic acid	-1.93	-0.54	1.39
31	squaric acid	-3.15	-2.41	0.74
32	thiourea	-4.02	-3.06	0.96
33	TDCPP	-3.25	-0.09	3.16
34	water	-2.92	-3.11	-0.19
35	urea	-3.15	-3.25	-0.10

3. Mouse skin – Predicted permeability using the Cronin et al. (1999) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp)- log K_p (Cronin) (cmh^{-1})
1	alachlor	-3.18	-2.51	0.67
2	atenolol	-1.52	-5.10	-3.58
3	atrazine	-3.11	-2.38	0.73
4	bisphenol A diglycidyl ether (BADGE)	-5.07	-2.88	2.19
5	n-butanol	-1.94	-2.45	-0.51
6	caffeine	-3.59	-4.21	-0.62
7	corticosterone	-3.28	-4.37	-1.09
8	coumarin	-3.00	-2.67	0.33
9	o-cresyl glycidyl ether (oCGE)	-3.75	-2.36	1.39
10	deoxycortisone	-2.47	-3.33	-0.86
11	dibutyl squarate	-3.07	-2.77	0.30
12	diethyl squarate	-3.00	-0.95	2.05
13	ethanol	-2.72	-2.91	-0.19
14	etorphine	-2.34	-4.24	-1.90
15	5-fluorouracil	-4.22	-4.29	-0.07
16	n-hexanol	-1.43	-1.82	-0.39
17	1,6-hexanediol diglycidyl ether (HDDGE)	-3.24	-4.05	-0.81
18	n-heptanol	-0.99	-2.13	-1.14
19	hydrocortisone	-4.00	-4.82	-0.82
20	17a-hydroxyprogesterone	-3.06	-3.36	-0.30
21	lidocaine	-2.05	-3.47	-1.41
22	N-N-diethyl m-toluamide	-2.46	-2.56	-0.10
23	methanol	-2.74	-3.15	-0.41
24	morphine	-3.82	-4.71	-0.89
25	nicorandil	-3.00	-4.17	-1.17
26	n-octanol	-1.01	-1.51	-0.50
27	prednisolone 21-heptanoate	-4.11	-3.66	0.45
28	progesterone	-1.96	-2.74	-0.78
29	propranolol HCL	-4.30	-4.80	-0.50
30	salicylic acid	-1.93	-2.03	-0.10
31	squaric acid	-3.15	-3.84	-0.69
32	thiourea	-4.02	-4.12	-0.10
33	TDCPP	-3.25	-3.96	-0.71
34	water	-2.92	-3.58	-0.66
35	urea	-3.15	-4.16	-1.01

4. Mouse skin – Predicted permeability using the revised Robinson (1995) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Robinson) (cmh^{-1})	Log K_p (exp)- log K_p (Robinson) (cmh^{-1})
1	alachlor	-3.18	-2.22	0.96
2	atenolol	-1.52	-4.19	-2.67
3	atrazine	-3.11	-2.24	0.87
4	bisphenol A diglycidyl ether (BADGE)	-5.07	-2.30	2.77
5	n-butanol	-1.94	-2.36	-0.42
6	caffeine	-3.59	-3.69	-0.10
7	corticosterone	-3.28	-3.43	-0.15
8	coumarin	-3.00	-2.57	0.43
9	o-cresyl glycidyl ether (oCGE)	-3.75	-2.31	1.44
10	deoxycortisone	-2.47	-2.68	-0.21
11	dibutyl squarate	-3.07	-2.53	0.54
12	diethyl squarate	-3.00	-1.30	1.70
13	ethanol	-2.72	-2.62	0.10
14	etorphine	-2.34	-3.11	-0.77
15	5-fluorouracil	-4.22	-3.82	0.40
16	n-hexanol	-1.43	-1.92	-0.49
17	1,6-hexanediol diglycidyl ether (HDDGE)	-3.24	-3.51	-0.27
18	n-heptanol	-0.99	-2.15	-1.16
19	hydrocortisone	-4.00	-3.72	0.28
20	17a-hydroxyprogesterone	-3.06	-2.70	0.36
21	lidocaine	-2.05	-3.05	-1.00
22	N-N-diethyl m-toluamide	-2.46	-2.43	0.03
23	methanol	-2.74	-2.72	0.02
24	morphine	-3.82	-3.87	-0.05
25	nicorandil	-3.00	-3.64	-0.64
26	n-octanol	-1.01	-1.69	-0.68
27	prednisolone 21-heptanoate	-4.11	-2.42	1.69
28	progesterone	-1.96	-2.27	-0.31
29	propranolol HCL	-4.30	-3.91	0.39
30	salicylic acid	-1.93	-2.08	-0.15
31	squaric acid	-3.15	-3.48	-0.33
32	thiourea	-4.02	-3.65	0.37
33	TDCPP	-3.25	-2.81	0.44
34	water	-2.92	-2.91	0.01
35	urea	-3.15	-3.63	-0.48

Mouse skin – Predicted permeability using the Barratt (1995b) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Barratt) (cmh^{-1})	Log K_p (exp)- log K_p (Barratt) (cmh^{-1})
1	alachlor	-3.18	-3.67	-0.49
2	atenolol	-1.52	-10.59	-9.07
3	atrazine	-3.11	-8.88	-5.77
4	bisphenol A diglycidyl ether (BADGE)	-5.07	-2.77	2.30
5	n-butanol	-1.94	1.14	3.08
6	caffeine	-3.59	-13.32	-9.73
7	corticosterone	-3.28	-11.09	-7.81
8	coumarin	-3.00	-5.23	-2.23
9	o-cresyl glycidyl ether (oCGE)	-3.75	-3.48	0.27
10	deoxycortisone	-2.47	-8.39	-5.92
11	dibutyl squarate	-3.07	-9.35	-6.28
12	diethyl squarate	-3.00	-5.74	-2.74

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Barratt) (cmh^{-1})	Log K_p (exp)- log K_p (Barratt) (cmh^{-1})
13	ethanol	-2.72	1.55	4.27
14	etorphine	-2.34	-12.10	-9.76
15	5-fluorouracil	-4.22	-15.19	-10.97
16	n-hexanol	-1.43	0.38	1.81
17	1,6-hexanediol diglycidyl ether (HDDGE)	-3.24	-7.12	-3.88
18	n-heptanol	-0.99	-0.62	0.37
19	hydrocortisone	-4.00	-12.98	-8.98
20	17a-hydroxyprogesterone	-3.06	-13.67	-10.61
21	lidocaine	-2.05	-5.79	-3.74
22	N-N-diethyl m-toluamide	-2.46	-0.53	1.93
23	methanol	-2.74	0.65	3.39
24	morphine	-3.82	-14.37	-10.55
25	nicorandil	-3.00	-7.58	-4.58
26	n-octanol	-1.01	-0.66	0.35
27	prednisolone 21-heptanoate	-4.11	-10.24	-6.13
28	progesterone	-1.96	-6.99	-5.03
29	propranolol HCL	-4.30	-13.59	-9.29
30	salicylic acid	-1.93	-7.97	-6.04
31	squaric acid	-3.15	-15.21	-12.06
32	thiourea	-4.02	-11.01	-6.99
33	TDCPP	-3.25	-4.43	-1.18
34	water	-2.92	-3.66	-0.74
35	urea	-3.15	-9.47	-6.32

For all of the above models, compounds 27-35 were eliminated due to log P values smaller than 3 and MW smaller than 500.

Figure 1. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Potts and Guy (n=35).

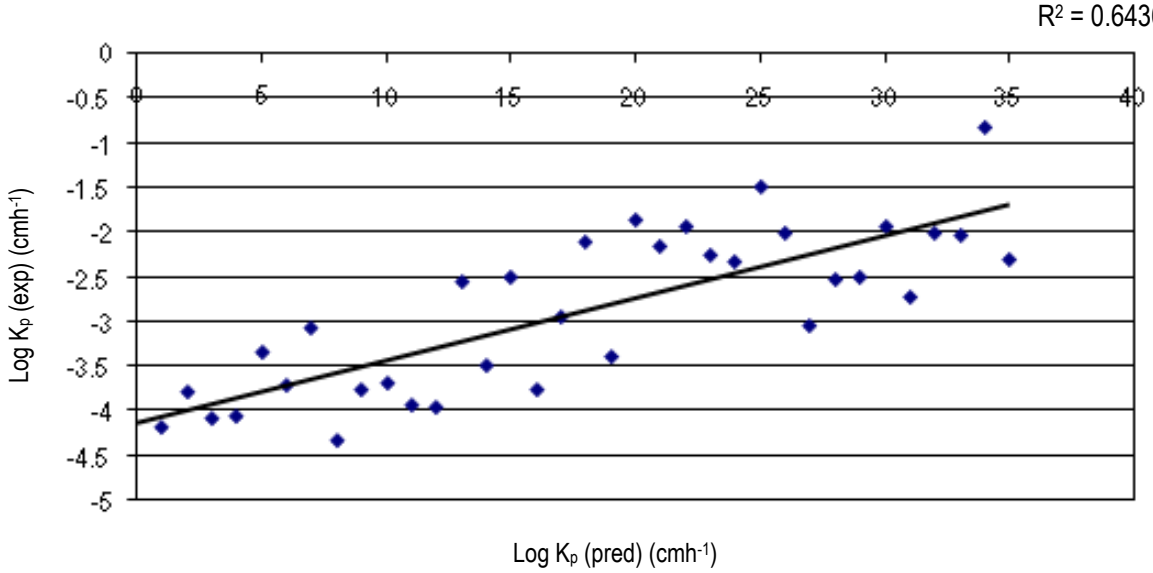


Figure 2. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Potts and Guy (n=26).

R^2= 0.3473

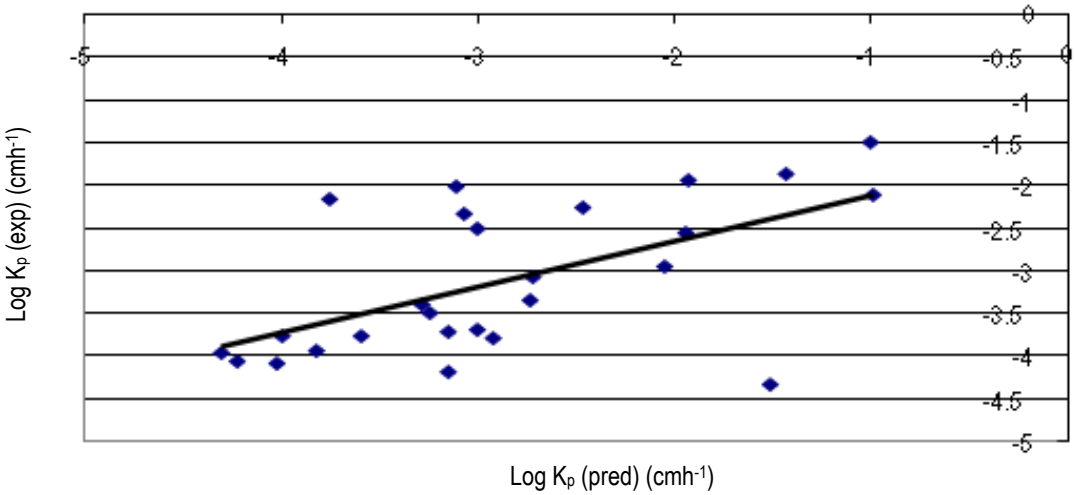


Figure 3. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Brown and Rossi (n=35).

R^2 = 0.0221

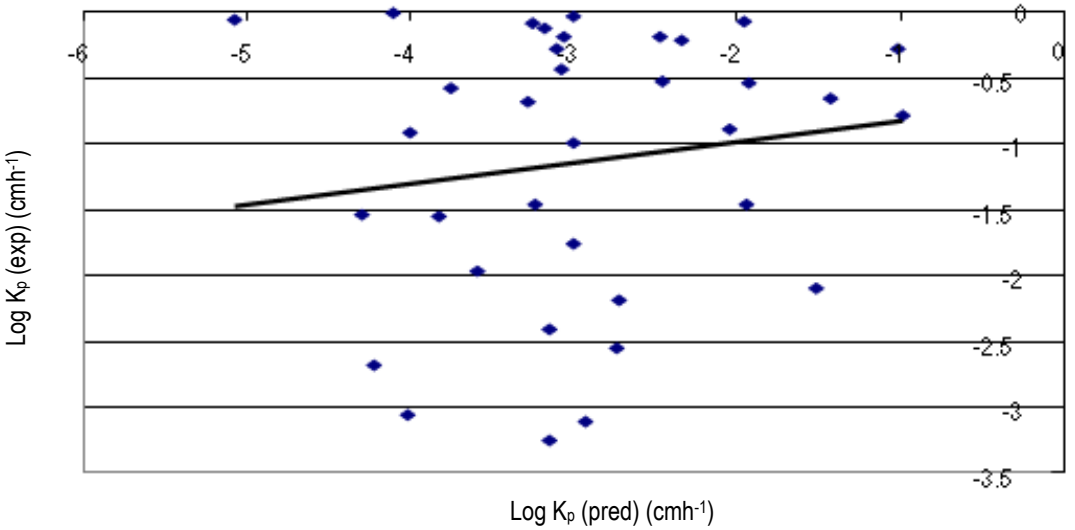


Figure 4. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Brown and Rossi (n=26).

R^2= 0.123

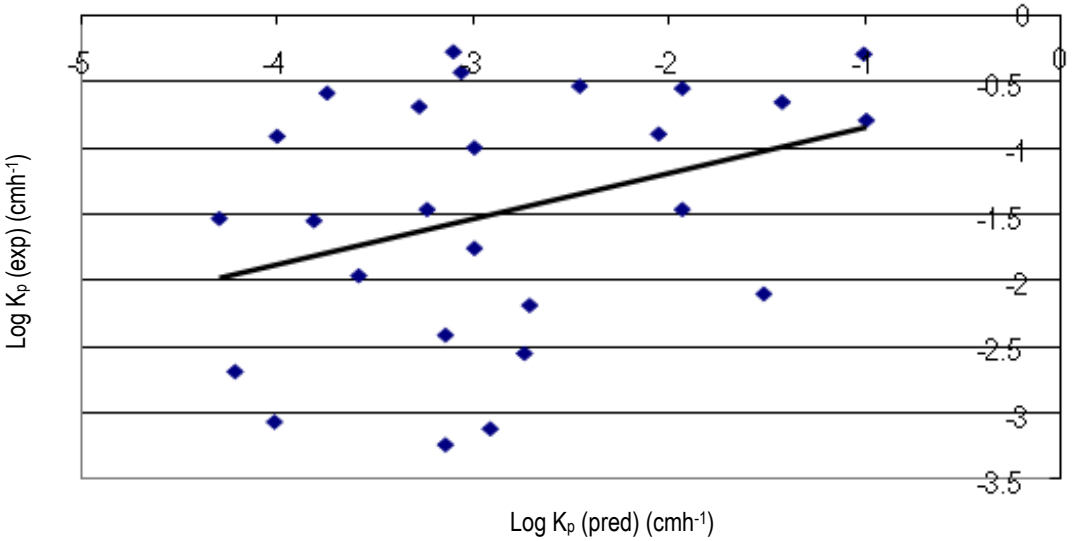


Figure 5. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Cronin (n=35).

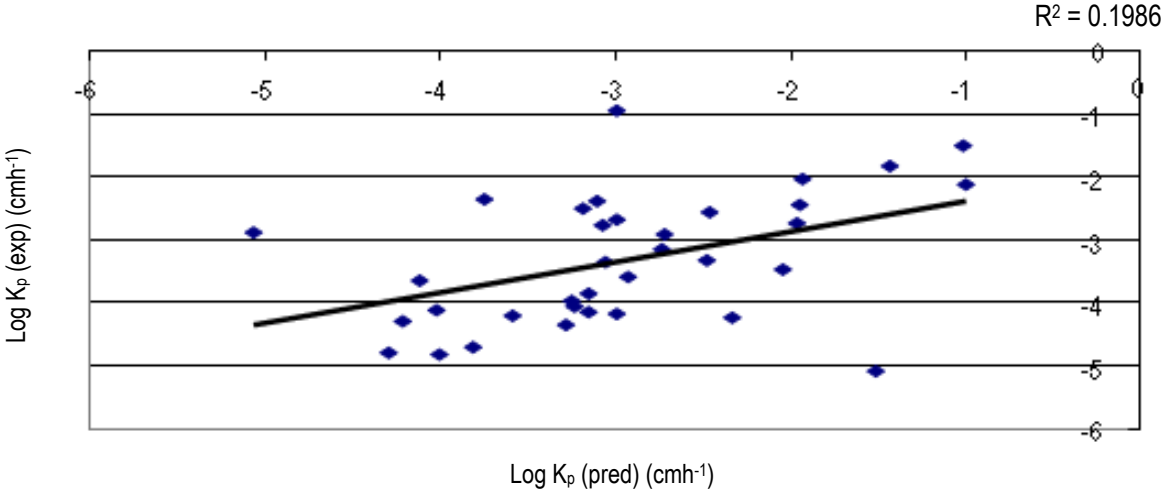


Figure 6. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Cronin (n=26).

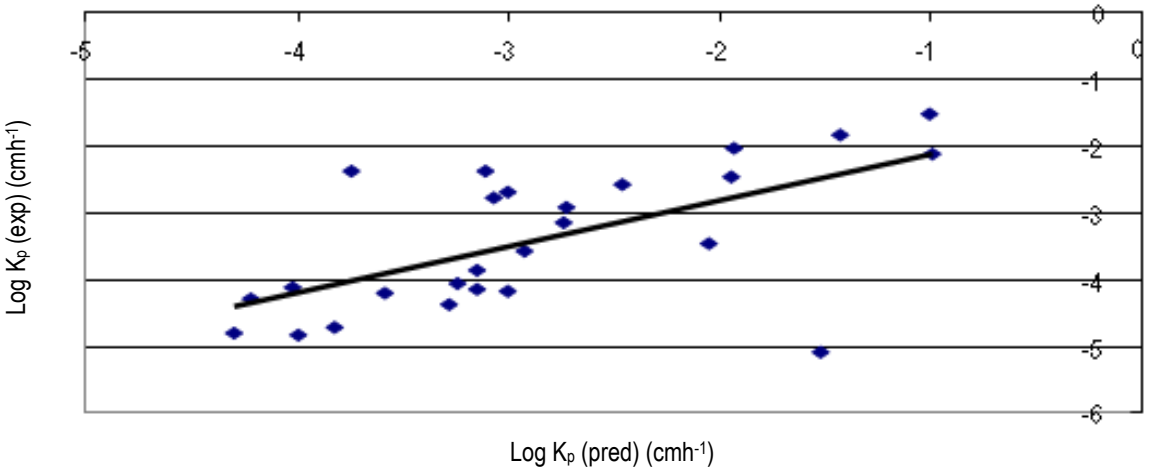


Figure 7. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Robinson (n=35).

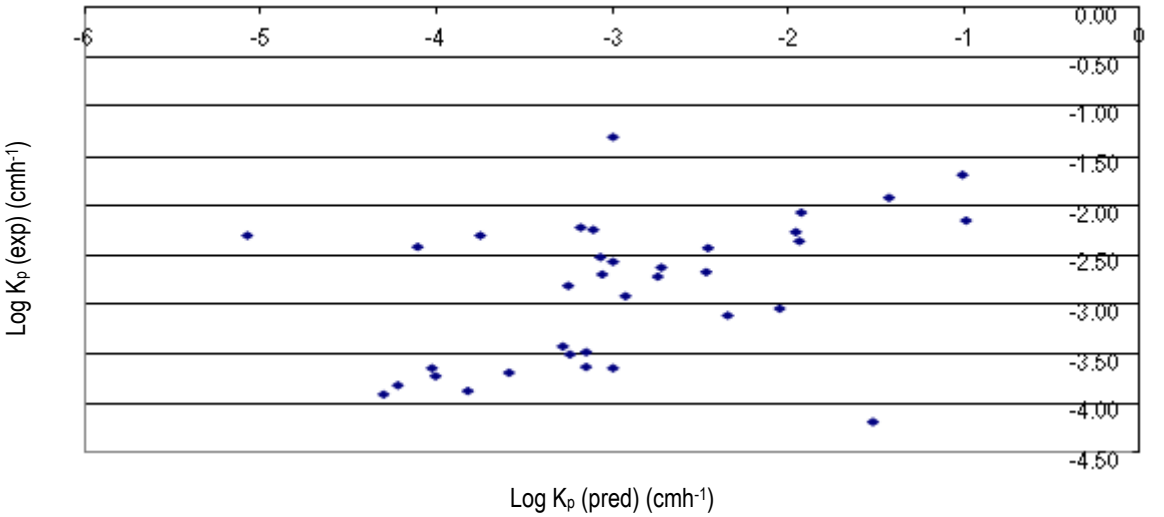


Figure 8. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Robinson (n=26).

R^2= 0.3831

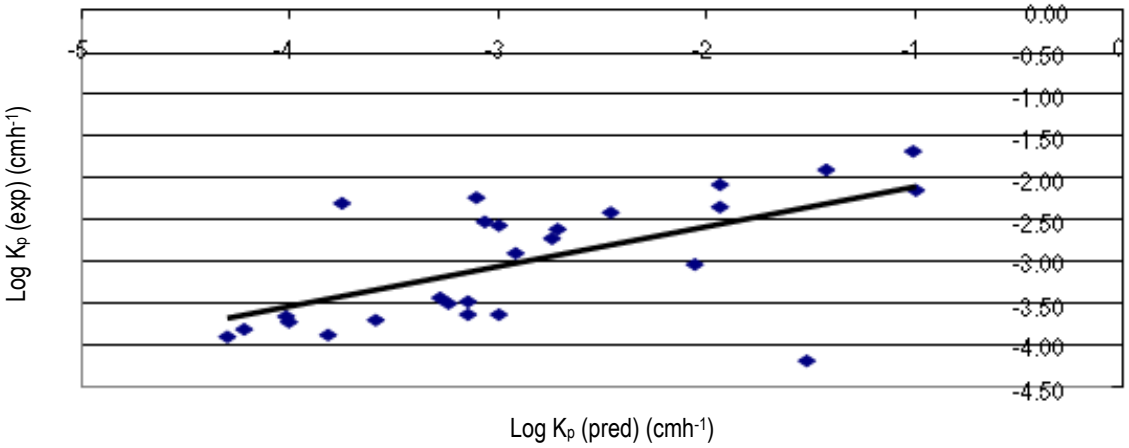


Figure 9. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Barratt (n=35).

R^2 = 0.2223

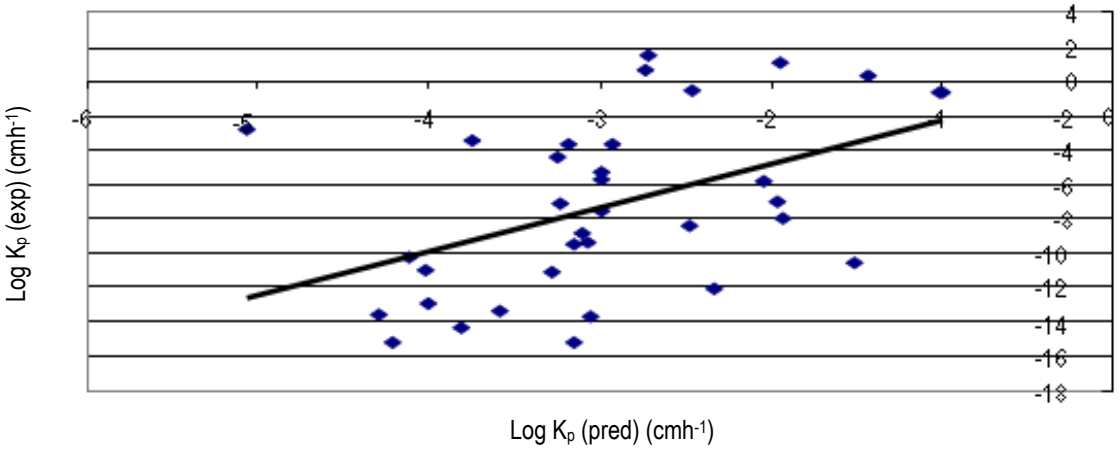
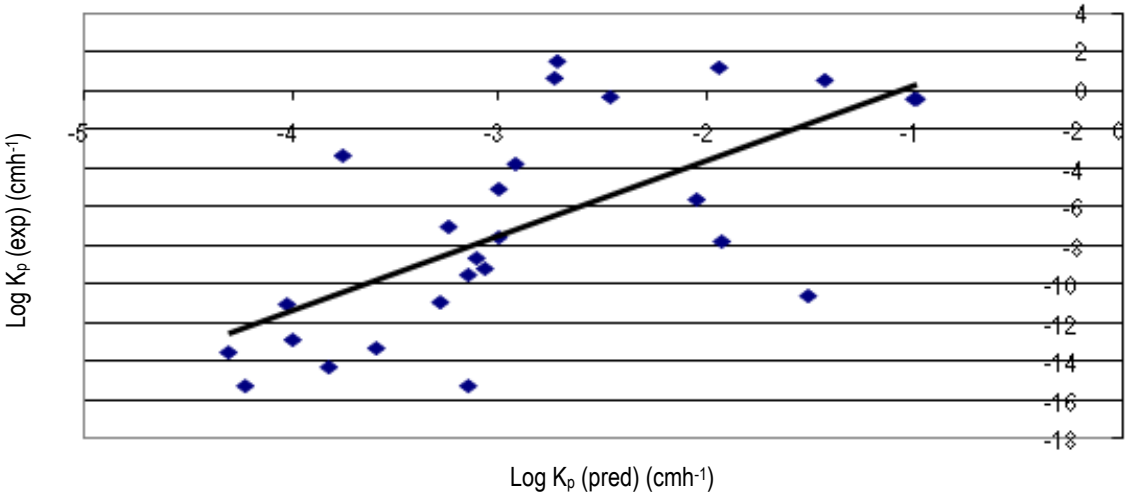


Figure 10. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Barratt (n=26).

R^2 = 0.4418



Appendix 17. Database C. Rat skin dataset – Experimental vs predicted K_p values

Rat skin dataset – Experimental permeability coefficients and drug properties

No	Name	MW	MPt (^{0}C)	Log P KOWWIN	Log K_p (cmh^{-1})	Journal
1	mannitol	182.17	138.97	-3.01	-3.64	*Pharm.Res.* 9, 884-887
2	paraquat	257.16	300.00	-2.71	-3.46	*J.Invest.Dermatol.* 96, 921-925
3	diethylene glycol monomethyl ether	120.20	-14.60	-1.50	-1.09	*Toxicol.* 55, 247-255
4	erioglaucine	793.86	283.00	-1.50	-4.12	*J.Pharm.Pharmacol.* 42, 468-472
5	water	18.02	0.00	-1.38	-2.70	*Toxicol. Vitro* 8, 827-830
6	2-(2-methoxyethoxy)ethanol	120.15	-70.00	-1.18	-1.10	*Toxicol.Sci.*55, 247-255
7	2-ethoxyethanol	90.12	-90.00	-0.42	-3.83	*Toxicol. Appl.Pharmacol.*180,74-82
8	theophylline	180.17	273.00	-0.39	-2.66	*J.Soc.Cosmet.Chem.* 40, 231-242
9	ethanol	46.07	-114.10	-0.14	-3.38	*J.Invest.Dermatol.* 96, 921-925
10	caffeine	194.20	238.00	0.16	-2.99	*Toxicology* 177, 65-66
11	scopolamine	303.40	59.00	0.39	-2.39	*J.Pharm.Sci.* 83, 29-32
12	nicorandil	211.18	92.50	0.43	-3.14	*J.Pharm.Pharmacol.*41, 379-383
13	aminopyrene	231.00	108.00	0.60	-1.48	*Int.J.Pharm.* 262,13-22
14	methyl nicotinate	137.14	42.50	0.64	-2.65	*J.Pharm.Sci.* 80, 54-56
15	2,4 dimethylamine	266.13	86.00	0.84	-3.51	*Toxicol.Vitro*11, 251-262
16	1,6-hexanediol diglycidyl ether (HDDGE)	230.20	84.83	0.84	-3.40	*Xenobiotica* 30, 469-483
17	hydroquinone	110.11	170.00	1.03	-4.66	*Toxicol.Lett.*80,167-172
18	salicylamide	137.14	140.00	1.03	-4.77	*Eur. J.Pharm.Sci.* 17, 95-104
19	aniline	93.00	-6.20	1.08	-1.17	*Int.J.Pharm.* 100,1-7
20	2-phenoxyethanol	138.17	14.00	1.10	-2.75	*Food Chem.Toxicol.*35,1009-1016
21	coumarin	146.15	70.60	1.51	-3.10	*Toxicol.Appl.Pharmacol.*145, 34-42
22	4-methylaniline	107.20	43.70	1.62	-1.07	*Int.J.Pharm.* 100,1-7
23	metochloropramide	354.30	182.00	1.69	-2.04	*J.Pharm.Sci.* 83, 29-32
24	alizapride	339.90	207.00	1.80	-2.24	*J.Pharm.Sci.* 83, 29-32
25	cortisone	360.50	220.00	1.81	-3.33	*J.Soc.Cosmet.Chem.* 34, 127-135
26	benzoic acid	122.10	122.00	1.87	-2.02	*Toxicol.Vitro* 12, 47-55
27	propoxur	209.25	87.00	1.90	-2.43	*Toxicol.Sci.* 58,15-22
28	bromopride	344.26	152.50	1.94	-2.11	*J.Pharm.Sci.* 83, 29-32
29	bufexamac	223.30	154.00	1.98	-0.57	*Int.J.Pharm.* 262, 13-22
30	benzyl acetate	150.18	-51.30	2.08	-3.57	*Food Chem.Toxicol.*28, 443-447
31	ethylaniline	121.20	-64.00	2.11	-0.94	*Int.J.Pharm.* 100, 1-7
32	o-cresyl glycidyl ether (oCGE)	164.20	30.25	2.16	-3.87	*Xenobiotica* 30, 469-483
33	salicylic acid	138.10	158.00	2.24	-1.98	*J.Pharm.Pharmacol.*45, 414-418
34	N-N-diethyl m-toluamide	191.28	-45.00	2.26	-2.77	*Toxicol.Vitro* 7,141-148
35	lorazepam	321.16	167.00	2.41	-3.25	*Int.J.Pharm.* 250, 359-369
36	metopimazine	445.61	170.50	2.42	-2.29	*J.Pharm.Sci.* 83, 29-32
37	triclosan	289.55	56.00	2.47	0.13	*J.Pharmacol.Exp.Ther.*38, 361-370
38	toluene (methyl benzene)	92.10	-94.90	2.54	-2.96	*Toxicol. Sci.* 55, 247-255
39	4-n-propylaniline	135.00	N/A	2.61	-0.77	*Int.J.Pharm.* 100, 1-7
40	DEP	222.24	-3.00	2.65	-3.43	*Environ.Health Perspect.*74, 223-227
41	nitrendipine	360.40	184.13	2.99	-2.41	*J.Pharm.Sci.* 80, 931-934
42	ethyl benzene	106.20	-94.90	3.03	-3.51	*Toxicol. Sci.* 55, 247-255
43	xylene (dimethyl benzene)	106.20	-50.00	3.09	-3.77	*Toxicol. Sci.* 55, 247-255
44	4-n-butylaniline	149.00	-14.00	3.10	-0.64	*Int.J.Pharm.* 100, 1-7
45	ketoprofen	254.29	94.00	3.12	-1.73	*Int.J.Pharm.* 262, 13-22
46	nimodipine	418.40	125.00	3.13	-2.59	*J.Pharm.Sci.* 80, 931-934
47	naphthalene	128.20	80.60	3.17	-3.29	*Toxicol.Sci.* 55, 247-255
48	clebopride	373.90	162.00	3.21	-2.13	*J.Pharm.Sci.* 83, 29-32
49	testosterone	288.40	155.00	3.27	-2.74	*J.Pharm.Pharmacol.* 52, 369-375
50	2-phenylphenol	170.21	59.00	3.28	-1.58	*Toxicol.Pharmacol.* 35,198-208
51	domperidone	425.92	242.50	3.35	-2.55	*J.Pharm.Sci.* 83, 29-32
52	4-n-pentylaniline	163.30	N/A	3.59	-0.61	*Int.J.Pharm.* 100,1-7
53	dinoseb	240.22	40.00	3.67	-2.94	*Fundam.Appl.Toxicol.*19, 258-267
54	bisphenol A diglycidyl ether (BADGE)	340.80	10.00	3.84	-5.26	*Xenobiotica* 30, 469-483
55	felodipine	384.30	283.00	3.86	-2.40	*J.Pharm.Sci.* 80, 931-934
56	nicardipine	479.54	136.00	3.90	-2.31	*J.Pharm.Sci.* 80, 931-934
57	nifedipine	346.30	172.00	4.04	-2.77	*J.Pharm.Sci.* 80, 931-934
58	butyl salicylate	194.23	-6.00	4.08	-4.70	*Eur.J.Pharm.Sci.* 17, 95-104
59	4-n-hexylaniline	177.30	N/A	4.08	-0.64	*Int.J.Pharm.* 100, 1-7
60	haloperidol	375.90	151.50	4.22	-1.70	*Int.J.Pharm* 212, 247-255
61	dodecyl decaethoxylate	482.90	N/A	4.33	-5.31	*Toxicol. Vitro* 12, 57-65
62	dodecyl monoethoxylate	230.40	N/A	4.50	-2.26	*Toxicol. Vitro* 12, 57-65
63	nonane	128.30	-53.50	4.76	-4.38	*Toxicol.Sci.* 55, 247-255

No	Name	MW	MPt (^{0}C)	Log P KOWWIN	Log K_p (cmh^{-1})	Journal
64	fenoxapropethyl	361.77	84.00	4.95	-3.15	*Toxicol. Vitro* 6, 53-59
65	dodecyl glycidyl ether (C12GE)	242.20	58.00	5.01	-4.54	*Xenobiotica* 30, 469-483
66	dibutylphthalate	277.35	-35.00	5.11	-4.05	*Environ.Health Perspect.* 74, 223-227
67	epikote YX4000	354.40	N/A	5.19	-1.01	*Xenobiotica* 30, 469-483
68	decane	142.30	-29.70	5.25	-4.03	*Toxicol.Sci.* 55, 247-255
69	mefenamic acid	241.29	230.00	5.28	-2.11	*Int.J.Pharm.* 262, 13-22
70	undecane	156.31	-25.60	5.74	-4.60	*Toxicol. Sci.* 55, 247-255
71	terbinafine	291.40	N/A	5.81	-1.26	*Int.J.Pharm.* 215, 51-56
72	dodecane	170.34	-9.60	6.23	-4.85	*Toxicol.* 55, 247-255
73	clotrimazole	344.85	148.00	6.26	-2.26	*Int.J.Pharm.* 215, 51-56
74	tridecane	185.40	-5.50	6.73	-4.82	*Toxicol. Sci.* 55, 247-255
75	DDT	354.49	108.50	6.79	-2.17	*Toxicol.Vitro* 8,1225-1232
76	linoleic acid	289.45	-5.00	7.51	-4.54	*J.Pharm.Pharmacol.* 34, 610-611
77	DEHP	390.57	-50.00	8.39	-3.02	*Toxicol.Vitro* 12, 47-55

The following compounds have been excluded because of log P and MW values outside the desired range (MW < 500 and log P < 5).

- Compounds 66-77, 5.

Predicted permeability coefficient(s) for rat skin using different models

1. Rat skin – Predicted permeability using the Potts and Guy (1992) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Potts & Guy) (cmh^{-1})	Log K_p (exp) – log K_p (Potts & Guy) (cmh^{-1})
1	mannitol	-3.64	-5.95	2.31
2	paraquat	-3.46	-6.19	2.73
3	diethylene glycol monomethyl ether	-1.09	-4.50	3.41
4	water	-2.70	-3.79	1.09
5	2-(2-methoxyethoxy)ethanol	-1.10	-4.27	3.17
6	2-ethoxyethanol	-3.83	-3.55	-0.28
7	theophylline	-2.66	-4.08	1.42
8	ethanol	-3.38	-3.08	-0.30
9	caffeine	-2.99	-3.77	0.78
10	scopolamine	-2.39	-4.27	1.88
11	nicorandil	-3.14	-3.68	0.54
12	aminopyrene	-1.48	-3.68	2.20
13	methyl nicotinate	-2.65	-3.08	0.43
14	2,4 dimethylamine	-3.51	-3.73	0.22
15	1,6-hexanediol diglycidyl ether (HDDGE)	-3.40	-3.51	0.11
16	hydroquinone	-4.66	-2.64	-2.02
17	salicylamide	-4.77	-2.81	-1.96
18	aniline	-1.17	-2.50	1.33
19	2-phenoxyethanol	-2.75	-2.76	0.01
20	coumarin	-3.10	-2.52	-0.58
21	4-methylaniline	-1.07	-2.20	1.13
22	metochloropramide	-2.04	-3.66	1.62
23	alizapride	-2.24	-3.50	1.26
24	cortisone	-3.33	-3.61	0.28
25	benzoic acid	-2.02	-2.12	0.10
26	propoxur	-2.43	-2.63	0.20
27	bromopride	-2.11	-3.42	1.31
28	bufexamac	-0.57	-2.66	2.09
29	benzyl acetate	-3.57	-2.14	-1.43
30	ethylaniline	-0.94	-1.94	1.00
31	o-cresyl glycidyl ether (oCGE)	-3.87	-2.17	-1.70
32	salicylic acid	-1.98	-1.95	-0.03

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Potts & Guy) (cmh^{-1})	Log K_p (exp) – log K_p (Potts & Guy) (cmh^{-1})
33	N-N-diethyl m-toluamide	-2.77	-2.26	-0.51
34	lorazepam	-3.25	-2.95	-0.30
35	metopimazine	-2.29	-3.70	1.41
36	triclosan	0.13	-2.71	2.84
37	toluene (methyl benzene)	-2.96	-1.46	-1.50
38	4-n-propylaniline	-0.77	-1.67	0.90
39	DEP	-3.43	-2.17	-1.26
40	nitrendipine	-2.41	-2.77	0.36
41	ethyl benzene	-3.51	-1.20	-2.31
42	xylene (dimethyl benzene)	-3.77	-1.15	-2.62
43	4-n-butylaniline	-0.64	-1.41	0.77
44	ketoprofen	-1.73	-2.04	0.31
45	nimodipine	-2.59	-3.03	0.44
46	naphthalene	-3.29	-1.23	-2.06
47	clebopride	-2.13	-2.70	0.57
48	testosterone	-2.74	-2.14	-0.60
49	2-phenylphenol	-1.58	-1.41	-0.17
50	domperidone	-2.55	-2.92	0.37
51	4-n-pentylaniline	-0.61	-1.15	0.54
52	dinoseb	-2.94	-1.56	-1.38
53	bisphenol A diglycidyl ether (BADGE)	-5.26	-2.05	-3.21
54	felodipine	-2.40	-2.30	-0.10
55	nicardipine	-2.31	-2.86	0.55
56	nifedipine	-2.77	-1.94	-0.83
57	butyl salicylate	-4.70	-0.99	-3.71
58	4-n-hexylaniline	-0.64	-0.88	0.24
59	haloperidol	-1.70	-2.00	0.30
60	dodecyl decaethoxylate	-5.31	-2.57	-2.74
61	dodecyl monoethoxylate	-2.26	-0.91	-1.35
62	nonane	-4.38	-0.10	-4.28
63	fenoxapropethyl	-3.15	-1.39	-1.76

The following compounds have been further excluded because of log P and MW values outside the desired range (MW < 500 and log P < 3).

- Compounds 42-63. The database was decreased from 65 chemicals down to 41 compounds.

2. Rat skin – Predicted permeability using the Cronin et al. (1999) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp)- log K_p (Cronin) (cmh^{-1})
1	mannitol	-3.64	-6.52	-2.88
2	paraquat	-3.46	-7.07	-3.61
3	diethylene glycol monomethyl ether	-1.09	-4.72	-3.63
4	water	-2.70	-3.58	-0.88
5	2-(2-methoxyethoxy)ethanol	-1.10	-4.48	-3.38
6	2-ethoxyethanol	-3.83	-3.58	0.25
7	theophylline	-2.66	-4.49	-1.83
8	ethanol	-3.38	-2.91	0.47
9	caffeine	-2.99	-4.21	-1.22
10	scopolamine	-2.39	-5.15	-2.76
11	nicorandil	-3.14	-4.17	-1.03
12	aminopyrene	-1.48	-4.25	-2.77
13	methyl nicotinate	-2.65	-3.25	-0.60

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp)- log K_p (Cronin) (cmh^{-1})
14	2,4 dimethylamine	-3.51	-4.42	-0.91
15	1,6-hexanediol diglycidyl ether (HDDGE)	-3.40	-4.05	-0.65
16	hydroquinone	-4.66	-2.67	1.99
17	salicylamide	-4.77	-2.95	1.82
18	aniline	-1.17	-2.46	-1.29
19	2-phenoxyethanol	-2.75	-2.91	-0.16
20	coumarin	-3.10	-2.67	0.43
21	4-methylaniline	-1.07	-2.19	-1.12
22	metochloropramide	-2.04	-4.68	-2.64
23	alizapride	-2.24	-4.44	-2.21
24	cortisone	-3.33	-4.65	-1.32
25	benzoic acid	-2.02	-2.15	-0.13
26	propoxur	-2.43	-3.02	-0.59
27	bromopride	-2.11	-4.38	-2.27
28	bufexamac	-0.57	-3.11	-2.54
29	benzyl acetate	-3.57	-2.28	1.29
30	ethylaniline	-0.94	-1.95	-1.01
31	o-cresyl glycidyl ether (oCGE)	-3.87	-2.36	1.51
32	salicylic acid	-1.98	-2.03	-0.05
33	N-N-diethyl m-toluamide	-2.77	-2.56	0.21
34	lorazepam	-3.25	-3.77	-0.53
35	metopimazine	-2.29	-5.06	-2.76
36	triclosan	0.13	-3.41	-3.54
37	toluene (methyl benzene)	-2.96	-1.32	1.64
38	4-n-propylaniline	-0.77	-1.71	-0.94
39	DEP	-3.43	-2.58	0.85
40	nitrendipine	-2.41	-3.74	-1.33
41	ethyl benzene	-3.51	-1.09	2.41
42	xylene (dimethyl benzene)	-3.77	-1.04	2.73
43	4-n-butylaniline	-0.64	-1.48	-0.84
44	ketoprofen	-1.73	-2.55	-0.82
45	nimodipine	-2.59	-4.23	-1.64
46	naphthalene	-3.29	-1.21	2.08
47	clebopride	-2.13	-3.71	-1.58
48	testosterone	-2.74	-2.77	-0.04
49	2-phenylphenol	-1.58	-1.56	0.02
50	domperidone	-2.55	-4.14	-1.59
51	4-n-pentylaniline	-0.61	-1.25	-0.64
52	dinoseb	-2.94	-1.98	0.96
53	bisphenol A diglycidyl ether (BADGE)	-5.26	-2.88	2.38
54	felodipine	-2.40	-3.32	-0.92
55	nicardipine	-2.31	-4.27	-1.96
56	nifedipine	-2.77	-2.79	-0.02
57	butyl salicylate	-4.70	-1.19	3.51
58	4-n-hexylaniline	-0.64	-1.01	-0.37
59	haloperidol	-1.70	-2.95	-1.25
60	dodecyl decaethoxylate	-5.31	-3.97	1.34
61	dodecyl monoethoxylate	-2.26	-1.24	1.02
62	nonane	-4.38	0.01	4.39
63	fenoxapropethyl	-3.15	-2.24	0.91

The following compounds have been also excluded because of log P and MW values outside the desired range (MW < 500 and log P < 3).

- Compounds 42-63. The database was decreased from 63 chemicals down to 41 compounds.

3. Rat skin – Predicted permeability using the revised Brown and Rossi (1995) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp)- log K_p (Brown & Rossi) (cmh^{-1})
1	mannitol	-3.64	-4.34	-0.70
2	paraquat	-3.46	-4.11	-0.65
3	diethylene glycol monomethyl ether	-1.09	-3.20	-2.11
4	water	-2.70	-3.11	-0.41
5	2-(2-methoxyethoxy)ethanol	-1.10	-2.96	-1.86
6	2-ethoxyethanol	-3.83	-2.40	1.43
7	theophylline	-2.66	-2.37	0.29
8	ethanol	-3.38	-2.19	1.19
9	caffeine	-2.99	-1.96	1.03
10	scopolamine	-2.39	-1.79	0.60
11	nicorandil	-3.14	-1.76	1.38
12	aminopyrene	-1.48	-1.64	-0.16
13	methyl nicotinate	-2.65	-1.61	1.04
14	2,4 dimethylamine	-3.51	-1.46	2.05
15	1,6-hexanediol diglycidyl ether (HDDGE)	-3.40	-1.46	1.94
16	hydroquinone	-4.66	-1.33	3.33
17	salicylamide	-4.77	-1.33	3.44
18	aniline	-1.17	-1.29	-0.12
19	2-phenoxyethanol	-2.75	-1.28	1.47
20	coumarin	-3.10	-0.99	2.11
21	4-methylaniline	-1.07	-0.92	0.15
22	metochloropramide	-2.04	-0.87	1.17
23	aizapride	-2.24	-0.80	1.44
24	cortisone	-3.33	-0.80	2.53
25	benzoic acid	-2.02	-0.76	1.26
26	propoxur	-2.43	-0.74	1.69
27	bromopride	-2.11	-0.72	1.39
28	bufexamac	-0.57	-0.69	-0.12
29	benzyl acetate	-3.57	-0.63	2.94
30	ethylaniline	-0.94	-0.62	0.32
31	o-cresyl glycidyl ether (oCGE)	-3.87	-0.59	3.28
32	salicylic acid	-1.98	-0.54	1.44
33	N-N-diethyl m-toluamide	-2.77	-0.53	2.24
34	lorazepam	-3.25	-0.46	2.79
35	metopimazine	-2.29	-0.45	1.84
36	triclosan	0.13	-0.43	-0.56
37	toluene (methyl benzene)	-2.96	-0.40	2.56
38	4-n-propylaniline	-0.77	-0.37	0.40
39	DEP	-3.43	-0.35	3.08
40	nitrendipine	-2.41	-0.23	2.18
41	ethyl benzene	-3.51	-0.22	3.29
42	xylene (dimethyl benzene)	-3.77	-0.20	3.57
43	4-n-butylaniline	-0.64	-0.20	0.44
44	ketoprofen	-1.73	-0.19	1.54
45	nimodipine	-2.59	-0.19	2.40
46	naphthalene	-3.29	-0.18	3.11
47	clebopride	-2.13	-0.17	1.96

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp)- log K_p (Brown & Rossi) (cmh^{-1})
48	testosterone	-2.74	-0.15	2.59
49	2-phenylphenol	-1.58	-0.15	1.43
50	domperidone	-2.55	-0.14	2.41
51	4-n-pentylaniline	-0.61	-0.09	0.52
52	dinoseb	-2.94	-0.08	2.86
53	bisphenol A diglycidyl ether (BADGE)	-5.26	-0.06	5.20
54	felodipine	-2.40	-0.06	2.34
55	nicardipine	-2.31	-0.06	2.25
56	nifedipine	-2.77	-0.05	2.72
57	butyl salicylate	-4.70	-0.04	4.66
58	4-n-hexylaniline	-0.64	-0.04	0.60
59	haloperidol	-1.70	-0.03	1.67
60	dodecyl decaethoxylate	-5.31	-0.03	5.28
61	dodecyl monoethoxylate	-2.26	-0.02	2.24
62	nonane	-4.38	-0.01	4.37
63	fenoxapropethyl	-3.15	-0.01	3.14

The following compounds have been also excluded because of log P and MW values outside the desired range (MW < 500 and log P < 3).

- Compounds 42-63. The database was decreased from 63 chemicals down to 41 compounds.

4. Rat skin – Predicted permeability using the revised Robinson (1995) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Robinson) (cmh^{-1})	Log K_p (exp)- log K_p (Robinson) (cmh^{-1})
1	mannitol	-2.24	-3.51	-1.27
2	paraquat	-1.48	-3.66	-2.18
3	diethylene glycol monomethyl ether	-2.02	-2.17	-0.15
4	water	-3.57	-2.26	1.31
5	2-(2-methoxyethoxy)ethanol	-5.26	-2.30	2.96
6	2-ethoxyethanol	-2.11	-3.45	-1.34
7	theophylline	-0.57	-2.79	-2.22
8	ethanol	-0.64	-1.67	-1.03
9	caffeine	-4.70	-1.43	3.27
10	scopolamine	-2.99	-3.69	-0.70
11	nicorandil	-2.13	-2.83	-0.70
12	aminopyrene	-3.33	-3.60	-0.27
13	methyl nicotinate	-3.10	-2.57	0.53
14	2,4 dimethylamine	-3.87	-2.31	1.56
15	1,6-hexanediol diglycidyl ether (HDDGE)	-3.43	-2.38	1.05
16	hydroquinone	-1.09	-4.11	-3.02
17	salicylamide	-3.51	-3.71	-0.20
18	aniline	-2.94	-1.89	1.05
19	2-phenoxyethanol	-5.31	-2.62	2.69
20	coumarin	-2.26	-1.41	0.85
21	4-methylaniline	-2.55	-2.97	-0.42
22	metochloropramide	-3.38	-2.62	0.76
23	alizapride	-0.94	-2.02	-1.08
24	cortisone	-3.51	-1.40	2.11
25	benzoic acid	-3.83	-3.27	0.56
26	propoxur	-2.40	-2.48	-0.08
27	bromopride	-3.15	-1.77	1.38
28	bufexamac	-1.70	-2.24	-0.54

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Robinson) (cmh^{-1})	Log K_p (exp)- log K_p (Robinson) (cmh^{-1})
29	benzyl acetate	-3.40	-3.51	-0.11
30	ethylaniline	-0.64	-1.34	-0.70
31	o-cresyl glycidyl ether (oCGE)	-4.66	-2.57	2.09
32	salicylic acid	-1.73	-2.29	-0.56
33	N-N-diethyl m-toluamide	-3.25	-3.06	0.19
34	lorazepam	-3.64	-4.86	-1.22
35	metopimazine	-1.07	-2.20	-1.13
36	triclosan	-2.65	-3.02	-0.37
37	toluene (methyl benzene)	-1.10	-3.95	-2.85
38	4-n-propylaniline	-2.04	-3.64	-1.60
39	DEP	-2.29	-3.61	-1.32
40	nitrendipine	-2.77	-2.43	0.34
41	ethyl benzene	-3.29	-1.48	1.81
42	xylene (dimethyl benzene)	-2.31	-2.86	-0.55
43	4-n-butylaniline	-3.14	-3.64	-0.50
44	ketoprofen	-2.77	-2.21	0.56
45	nimodipine	-2.59	-3.07	-0.48
46	naphthalene	-2.41	-2.90	-0.49
47	clebopride	-4.38	-0.87	3.51
48	testosterone	-3.46	-4.96	-1.50
49	2-phenylphenol	-0.61	-1.50	-0.89
50	domperidone	-2.75	-2.76	-0.01
51	4-n-pentylaniline	-1.58	-1.70	-0.12
52	dinoseb	-0.77	-1.84	-1.07
53	bisphenol A diglycidyl ether (BADGE)	-2.43	-2.75	-0.32
54	felodipine	-4.77	-2.79	1.98
55	nicardipine	-1.98	-2.08	-0.10
56	nifedipine	-2.39	-4.14	-1.75
57	butyl salicylate	-2.74	-2.38	0.36
58	4-n-hexylaniline	-2.66	-3.92	-1.26
59	haloperidol	-2.96	-1.54	1.42
60	dodecyl decaethoxylate	0.13	-2.86	-2.99
61	dodecyl monoethoxylate	-3.77	-1.37	2.40
62	nonane	-2.70	-2.91	-0.21
63	fenoxapropethyl	-4.80	-3.63	1.17

The following compounds have also been excluded because of log P and MW values outside the desired range (MW < 500 and log P < 3).

- Compounds 42-63. The database was decreased from 63 chemicals down to 41 compounds.

5. Rat skin – Predicted permeability using the Barratt (1995b) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Barratt) (cmh^{-1})	Log K_p (exp)- log K_p (Barratt) (cmh^{-1})
1	paraquat	-3.46	-18.67	-15.21
2	diethylene glycol monomethyl ether	-1.09	-4.14	-3.05
3	water	-2.70	-3.66	-0.96
4	2-(2-methoxyethoxy)ethanol	-1.10	-1.71	-0.62
5	2-ethoxyethanol	-3.83	-0.03	3.80
6	theophylline	-2.66	-15.00	-12.34
7	ethanol	-3.38	1.55	4.93
8	caffeine	-2.99	-13.32	-10.33
9	scopolamine	-2.39	-7.16	-4.77

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Barratt) (cmh^{-1})	Log K_p (exp)- log K_p (Barratt) (cmh^{-1})
10	nicorandil	-3.14	-7.58	-4.44
11	aminopyrene	-1.48	-8.23	-6.75
12	methyl nicotinate	-2.65	-4.77	-2.12
13	2,4 dimethylamine	-3.51	-7.50	-3.99
14	1,6-hexanediol diglycidyl ether (HDDGE)	-3.40	-7.12	-3.72
15	hydroquinone	-4.66	-9.17	-4.51
16	salicylamide	-4.77	-8.25	-3.48
17	aniline	-1.17	-2.10	-0.93
18	2-phenoxyethanol	-2.75	-3.29	-0.54
19	coumarin	-3.10	-5.23	-2.13
20	4-methylaniline	-1.07	-3.73	-2.66
21	metochloropramide	-2.04	-11.37	-9.33
22	alizapride	-2.24	-12.12	-9.88
23	cortisone	-3.33	-12.81	-9.48
24	benzoic acid	-2.02	-6.72	-4.70
25	propoxur	-2.43	-6.14	-3.71
26	bromopride	-2.11	-9.92	-7.81
27	bufexamac	-0.57	-8.82	-8.25
28	benzyl acetate	-3.57	-0.05	3.52
29	ethylaniline	-0.94	0.74	1.68
30	o-cresyl glycidyl ether (oCGE)	-3.87	-3.30	0.57
31	salicylic acid	-1.98	-7.97	-5.99
32	N-N-diethyl m-toluamide	-2.77	-0.53	2.24
33	lorazepam	-3.25	-9.88	-6.63
34	metopimazine	-2.29	-11.17	-8.88
35	triclosan	0.13	-5.21	-5.34
36	toluene (methyl benzene)	-2.96	2.57	5.53
37	DEP	-3.43	-2.14	1.29
38	nitrendipine	-2.41	-10.44	-8.03
39	ethyl benzene	-3.51	2.84	6.35
40	xylene (dimethyl benzene)	-3.77	1.14	4.91
41	4-n-butylaniline	-0.64	-0.66	-0.02
42	ketoprofen	-1.73	-5.83	-4.10
43	nimodipine	-2.59	-8.56	-5.97
44	naphthalene	-3.29	-4.10	-0.81
45	clebopride	-2.13	-9.52	-7.39
46	testosterone	-2.74	-8.41	-5.67
47	2-phenylphenol	-1.58	-3.55	-1.97
48	domperidone	-2.55	-13.03	-10.48
49	dinoseb	-2.94	-3.14	-0.20
50	bisphenol A diglycidyl ether (BADGE)	-5.26	-2.77	2.49
51	felodipine	-2.40	-13.81	-11.41
52	nicardipine	-2.31	-8.93	-6.62
53	nifedipine	-2.77	-8.98	-6.21
54	butyl salicylate	-4.70	-0.59	4.11
55	haloperidol	-1.70	-8.30	-6.60
56	nonane	-4.38	2.44	6.82
57	fenoxapropethyl	-3.15	-4.94	-1.79

The following compounds have been excluded because of log P and MW values outside the desired range (MW < 500 and log P < 3).

- Compounds 39-57.

Figure 1. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Potts and Guy (n = 63).

R^2 = 0.0099

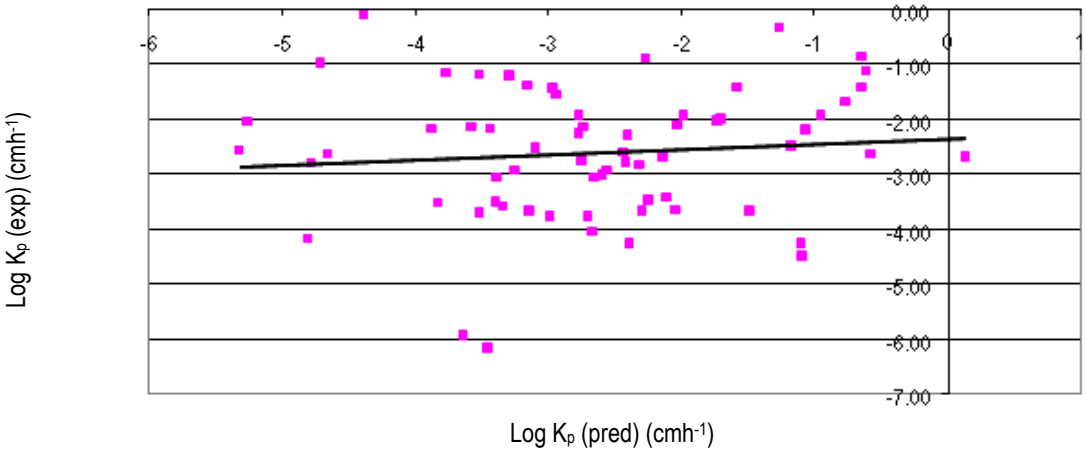


Figure 2. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Potts and Guy (n = 41).

R^2= 0.0393

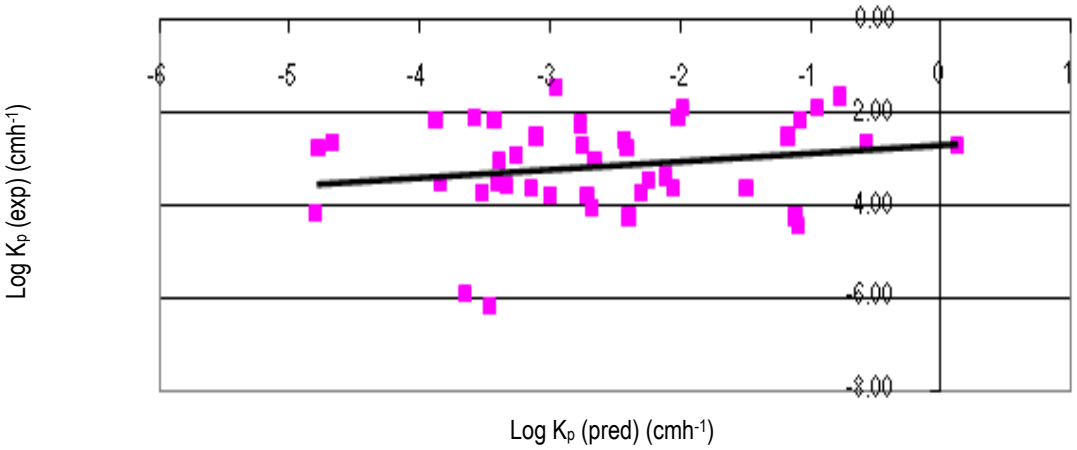


Figure 3. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Cronin (n = 63).

R^2 = 0.0044

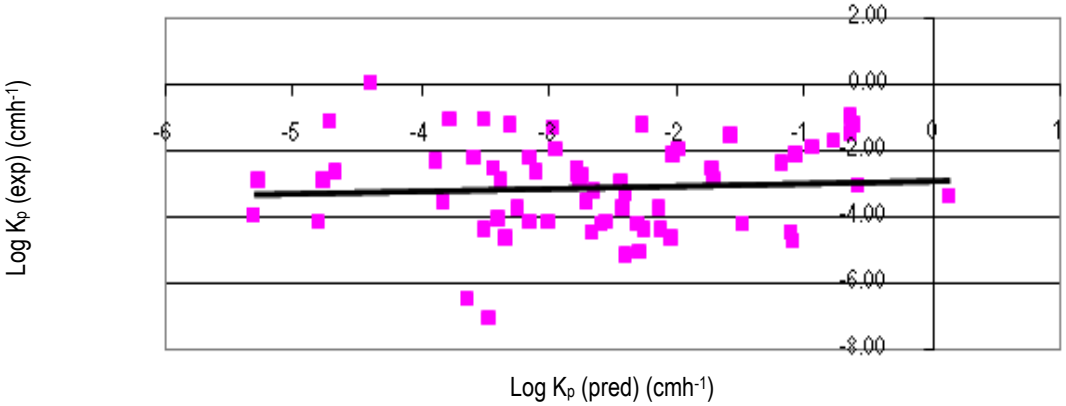


Figure 4. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Cronin (n = 41).

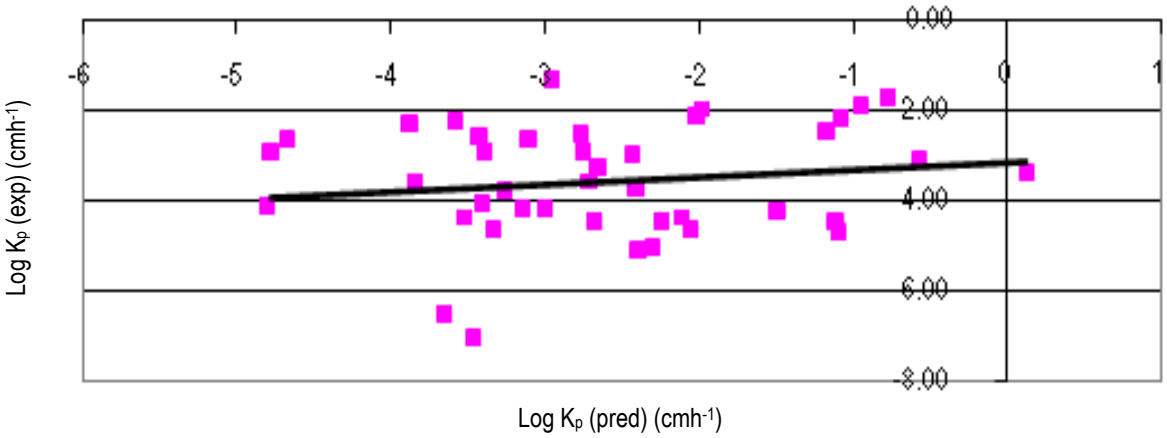


Figure 5. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Brown and Rossi (n = 63).

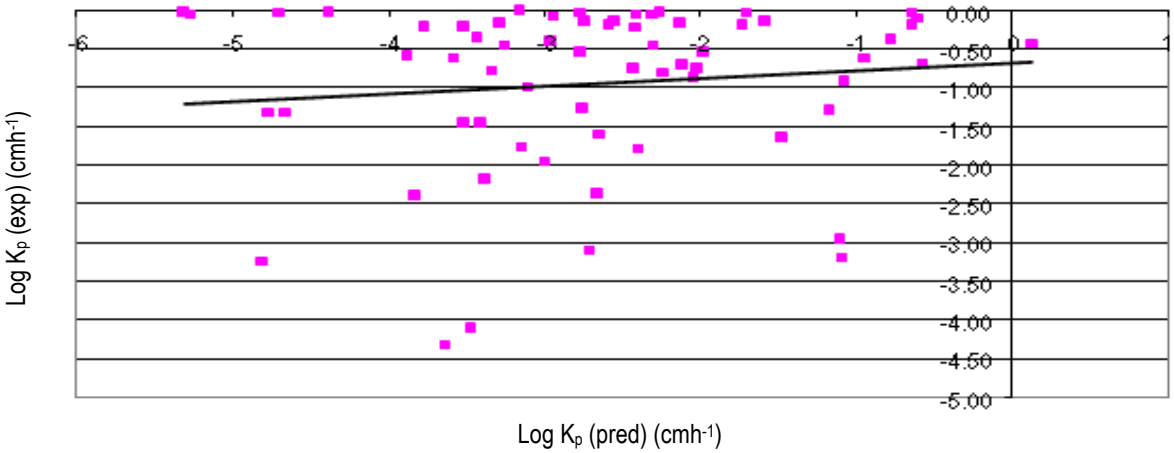


Figure 6. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Brown and Rossi (n = 41).

$R^2 = 0.0638$

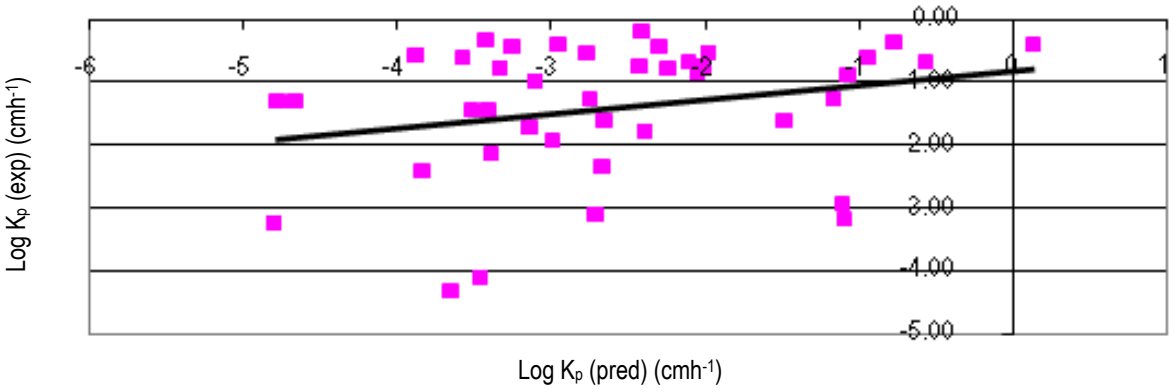


Figure 7. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Robinson (n = 63).

$R^2 = 0.0022$

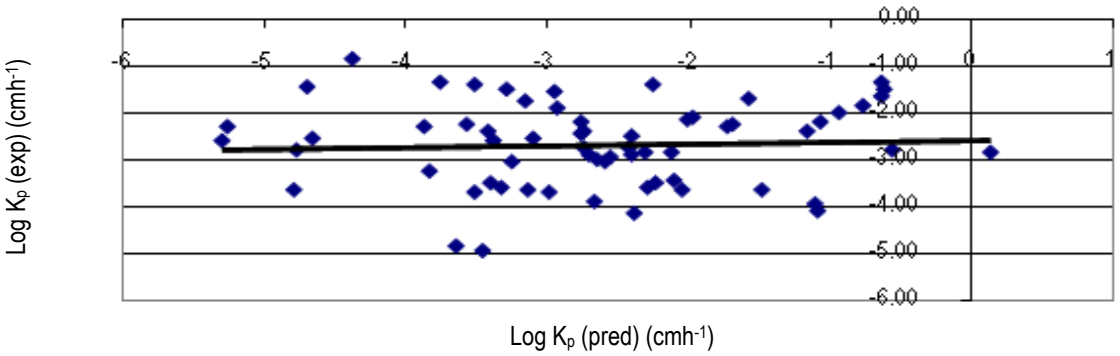


Figure 8. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Robinson (n = 41).

$R^2 = 0.0237$

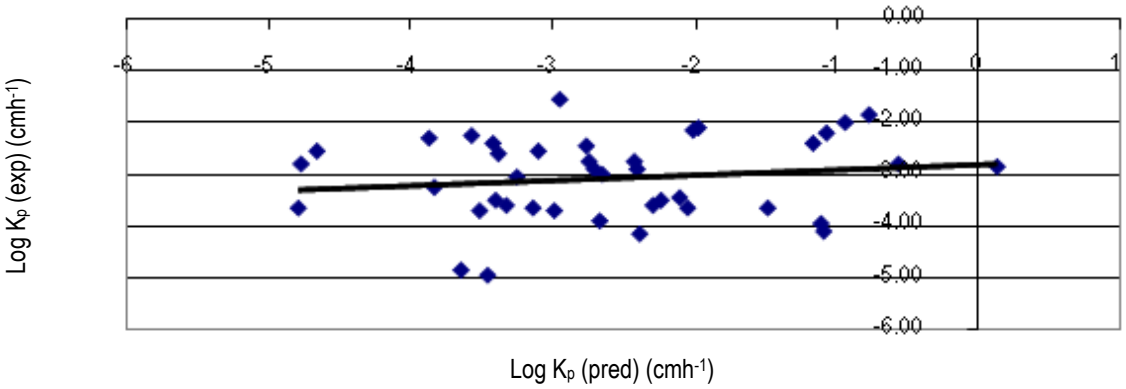


Figure 9. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Barratt (n = 57).

$R^2 = 0.005$

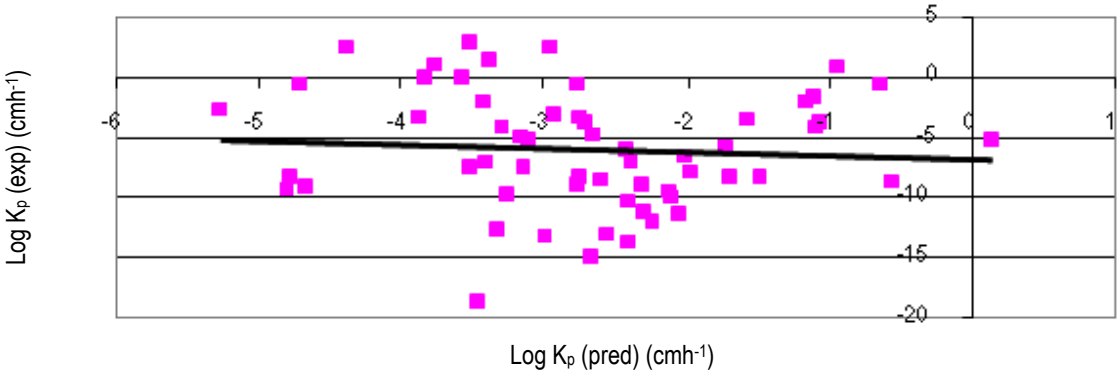
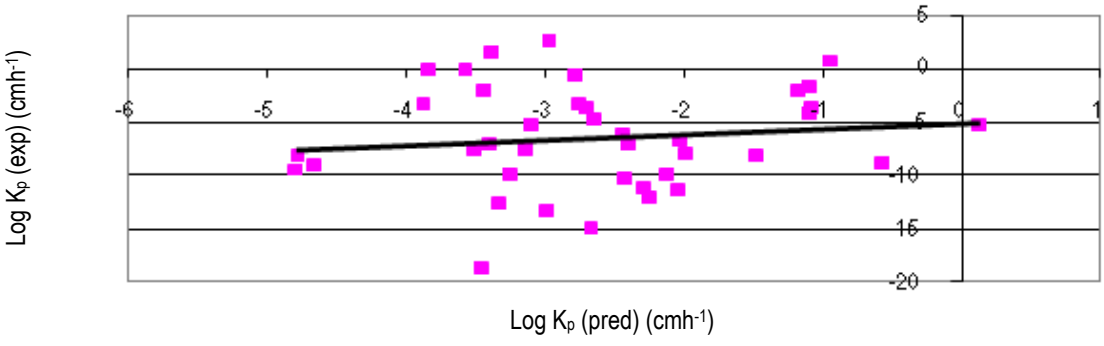


Figure 10. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Barratt (n = 39).

$R^2 = 0.0141$



Appendix 18. Database C. Pig skin dataset – Experimental vs predicted K_p values

Pig skin dataset – Experimental permeability coefficients and drug properties

No	Name	MW	MPt (^{0}C)	Log P KOWWIN	Log K_p (cmh^{-1})	Journal
1	mannitol	289.38	122.50	-3.01	-2.82	*Pharm. Res.* 15: 145-148
2	water	182.17	0.00	-1.38	-2.65	*Toxicol.Vitro* 8: 827-830
3	chlorogenic acid	170.21	208.00	-1.00	-2.62	*Reg.Toxicol.Pharmacol*. 35: 198-208
4	scopolamine	138.10	59.00	0.39	-6.29	*Int.J.Pharm*. 215: 51-56
5	caprtopril	303.40	127.00	0.84	-2.83	*J.Pharm.Pharmacology*, 58: 167-177
6	cafeic acid	291.40	224.00	1.10	-2.80	*Int.J.Pharm*. 215: 51-56
7	tropicamide	284.40	96.50	1.19	-6.15	*Pharm. Res*. 15: 145-148
8	atropine	18.02	118.00	1.91	-5.75	*Toxicol.Vitro* 8: 827-830
9	ligustrazine hydrochloride	217.29	88.00	2.18	-2.77	*J.Pharm.Pharmacology* 58: 167-177
10	salicylic acid	231.29	158.00	2.24	0.10	*J.Pharm.Pharmacology* 58: 167-177
11	methyl ester	245.29	138.00	2.90	-2.44	*J.Pharm.Pharmacology*, 58: 167-177
12	2-phenylphenol	259.00	56.00	3.28	-1.80	*J.Pharm.Pharmacology* 58: 167-177
13	ethyl ester	273.29	133.00	3.39	-2.09	*J.Pharm.Pharmacology*, 58: 167-177
14	propyl ester	287.29	190.00	3.89	-1.91	*J.Pharm.Pharmacology*, 58: 167-177
15	butyl ester	301.29	150.00	4.38	-1.97	*J.Pharm.Pharmacology*, 58: 167-177
16	pentyl ester	136.10	291.40	4.87	-2.97	*J.Pharm.Pharmacology*, 58: 167-177
17	pentachlorophenol	180.20	108.50	5.12	-2.32	*Int.J.Pharm*. 331: 139-144
18	hexyl ester	354.30	148.00	5.36	-2.91	*J.Pharm.Pharmacology*, 58: 167-177
19	terbinafine	266.33	196.50	5.81	-3.00	*Tox.Sciences* 69 (2007): 295-305
20	ketoprofen	254.29	94.00	0.97	-3.68	*Skin Pharmacol. Physiol.* 23 (2010): 113-16

Predicted permeability coefficient(s) for pig skin using different models

1. Pig skin – Predicted permeability using the Potts and Guy (1992) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Potts & Guy) (cmh^{-1})	Log K_p (exp)- log K_p (Potts & Guy) (cmh^{-1})
1	mannitol	-2.82	-5.95	-3.13
2	water	-2.65	-3.79	-1.14
3	chlorogenic acid	-2.62	-5.57	-2.95
4	scopolamine	-6.29	-4.27	2.02
5	caprtopril	-2.83	-3.43	-0.60
6	cafeic acid	-2.80	-3.02	-0.22
7	tropicamide	-6.15	-3.59	2.56
8	atropine	-5.75	-3.11	2.64
9	ligustrazine hydrochloride	-2.77	-1.98	0.79
10	salicylic acid	0.10	-1.95	-2.05
11	methyl ester	-2.44	-2.05	0.39
12	2-phenylphenol	-1.80	-1.41	0.39
13	ethyl ester	-2.09	-1.79	0.30
14	propyl ester	-1.91	-1.52	0.39
15	butyl ester	-1.97	-1.26	0.71
16	pentyl ester	-2.97	-0.99	1.98
17	pentachlorophenol	-2.32	-0.69	1.63
18	hexyl ester	-2.91	-0.73	2.18
19	terbinafine	-3.00	-0.35	2.65
20	ketoprofen	-3.68	-2.68	1.00

2. Pig skin – Predicted permeability using the revised Robinson (1995) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Robinson) (cmh^{-1})	Log K_p (exp)- log K_p (Robinson) (cmh^{-1})
1	mannitol	-2.82	-2.17	-1.10
2	water	-2.65	-3.69	-1.99
3	chlorogenic acid	-2.62	-1.15	-1.42
4	scopolamine	-6.29	-1.04	1.11
5	caprtopril	-2.83	-1.46	1.05
6	cafeic acid	-2.80	-2.08	-2.74
7	tropicamide	-6.15	-1.13	0.43
8	atropine	-5.75	-2.38	-0.84
9	ligustrazine hydrochloride	-2.77	-2.40	3.42
10	salicylic acid	0.10	-2.86	4.08
11	methyl ester	-2.44	-2.53	3.34
12	2-phenylphenol	-1.80	-2.19	4.00
13	ethyl ester	-2.09	-2.20	4.27
14	propyl ester	-1.91	-3.44	-1.04
15	butyl ester	-1.97	-2.29	0.02
16	pentyl ester	-2.97	-2.08	-0.08
17	pentachlorophenol	-2.32	-1.87	-0.22
18	hexyl ester	-2.91	-1.67	-0.29
19	terbinafine	-3.00	-1.49	-0.32
20	ketoprofen	-3.68	-2.76	-1.04

3. Pig skin – Predicted permeability using the revised Brown and Rossi (1995) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Brown & Rossi) (cmh^{-1})	Log K_p (exp)- log K_p (Brown & Rossi) (cmh^{-1})
1	atropine	-5.75	-0.74	5.01
2	mannitol	-2.82	-4.34	-1.52
3	2-phenylphenol	-1.80	-0.15	1.65
4	salicylic acid	0.10	-0.54	-0.64
5	scopolamine	-6.29	-1.79	4.50
6	terbinafine	-3.00	0.00	3.00
7	tropicamide	-6.15	-1.21	4.94
8	water	-2.65	-3.11	-0.46
9	caprtopril	-2.83	-1.46	1.37
10	methyl ester	-2.44	-0.26	2.18
11	ethyl ester	-2.09	-0.13	1.96
12	propyl ester	-1.91	-0.06	1.85
13	butyl ester	-1.97	-0.03	1.94
14	pentyl ester	-2.97	-0.01	2.96
15	hexyl ester	-2.91	0.00	2.91
16	ligustrazine hydrochloride	-2.77	-0.58	2.19
17	cafeic acid	-2.80	-1.28	1.52
18	chlorogenic acid	-2.62	-2.83	-0.21
19	pentachlorophenol	-2.32	-0.01	2.31
20	ketoprofen	-3.68	-2.01	-1.67

4. Pig skin – Predicted permeability using the Cronin et al. (1999) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp)- log K_p (Cronin) (cmh^{-1})
1	atropine	-5.75	-3.84	1.91
2	mannitol	-2.82	-6.52	-3.70
3	2-phenylphenol	-1.80	-1.56	0.24
4	salicylic acid	0.10	-2.03	-2.13
5	scopolamine	-6.29	-5.15	1.14
6	terbinafine	-3.00	-0.86	2.14
7	tropicamide	-6.15	-4.34	1.81
8	water	-2.65	-3.58	-0.93
9	caprtopril	-2.83	-3.92	-1.09
10	methyl ester	-2.44	-2.48	-0.04
11	ethyl ester	-2.09	-2.25	-0.16
12	propyl ester	-1.91	-2.01	-0.10
13	butyl ester	-1.97	-1.77	0.20
14	pentyl ester	-2.97	-1.54	1.43
15	hexyl ester	-2.91	-1.31	1.60
16	ligustrazine hydrochloride	-2.77	-2.05	0.72
17	cafeic acid	-2.80	-3.34	-0.54
18	chlorogenic acid	-2.62	-6.75	-4.13
19	pentachlorophenol	-2.32	-1.13	1.19
20	ketoprofen	-3.68	-2.11	-1.57

5. Pig skin – Predicted permeability using the Barratt (1995b) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Barratt) (cmh^{-1})	Log K_p (exp)- log K_p (Barratt) (cmh^{-1})
1	atropine	-5.75	-7.01	-1.26
2	mannitol	-2.82	-11.83	-9.01
3	2-phenylphenol	-1.80	-3.26	-1.46
4	salicylic acid	0.10	-9.51	-9.61
5	scopolamine	-6.29	-7.05	-0.76
6	terbinafine	-3.00	-0.24	2.76
7	tropicamide	-6.15	-5.32	0.83
8	water	-2.65	-5.51	-2.86
9	caprtopril	-2.83	-7.96	-5.13
10	methyl ester	-2.44	-6.90	-4.46
11	ethyl ester	-2.09	-6.09	-4.00
12	propyl ester	-1.91	-6.24	-4.33
13	butyl ester	-1.97	-6.39	-4.42
14	pentyl ester	-2.97	-6.55	-3.58
15	hexyl ester	-2.91	-5.08	-2.17
16	ligustrazine hydrochloride	-2.77	-6.67	-3.90
17	cafeic acid	-2.80	-13.45	-10.65
18	chlorogenic acid	-2.62	-13.73	-11.11
19	pentachlorophenol	-2.32	-5.57	-3.25
20	ketoprofen	-3.68	-2.29	-1.39

Figure 1. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Potts and Guy.

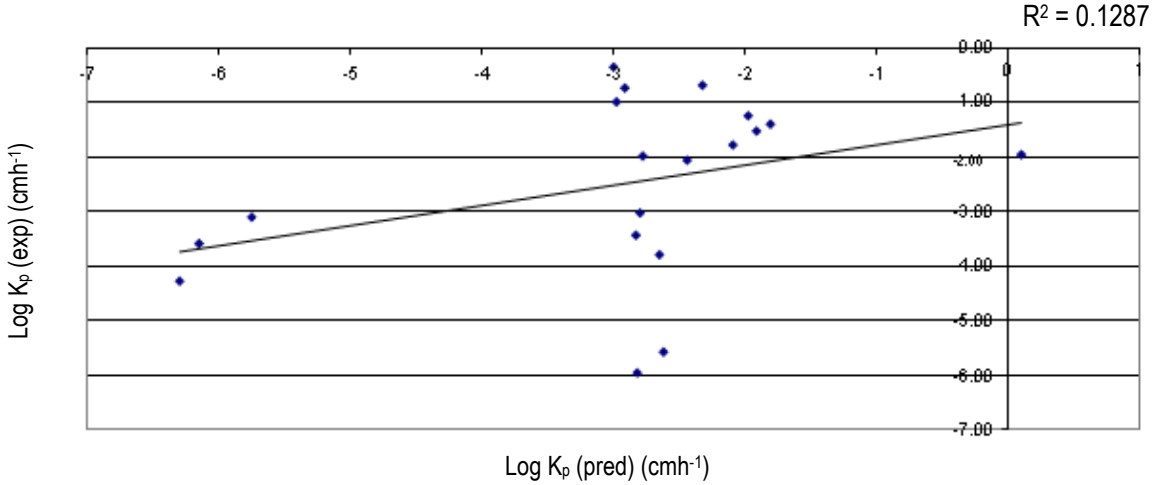


Figure 2. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Robinson.

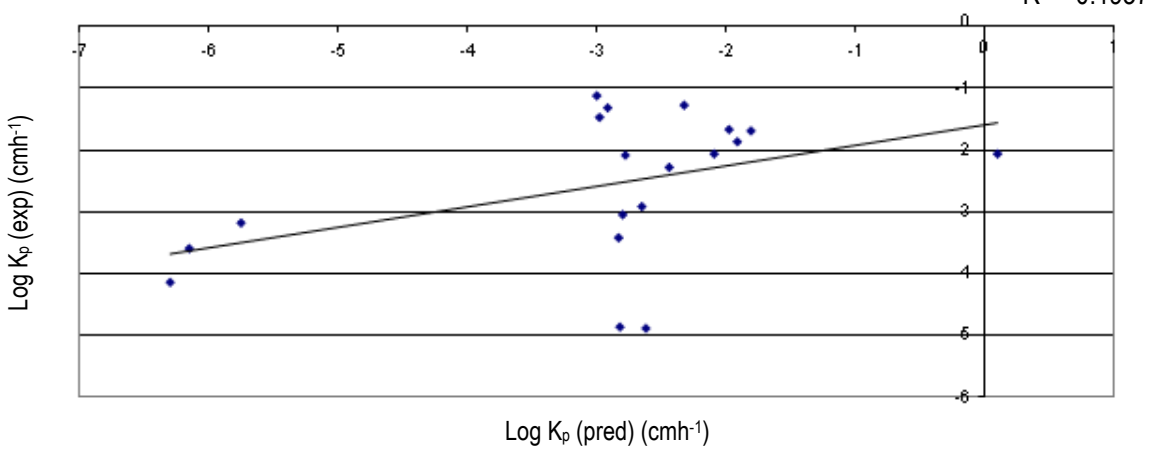


Figure 3. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Brown and Rossi.

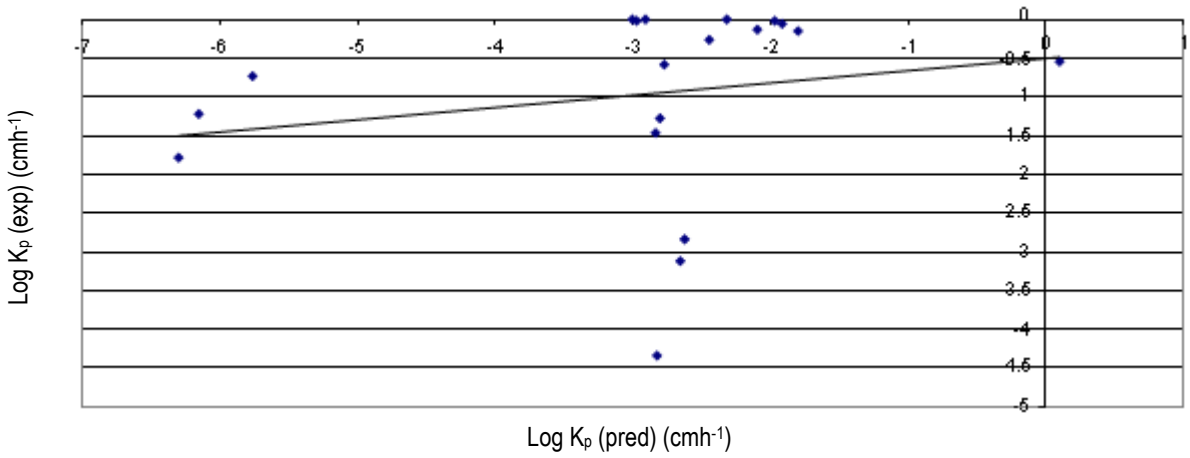


Figure 4. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Cronin.

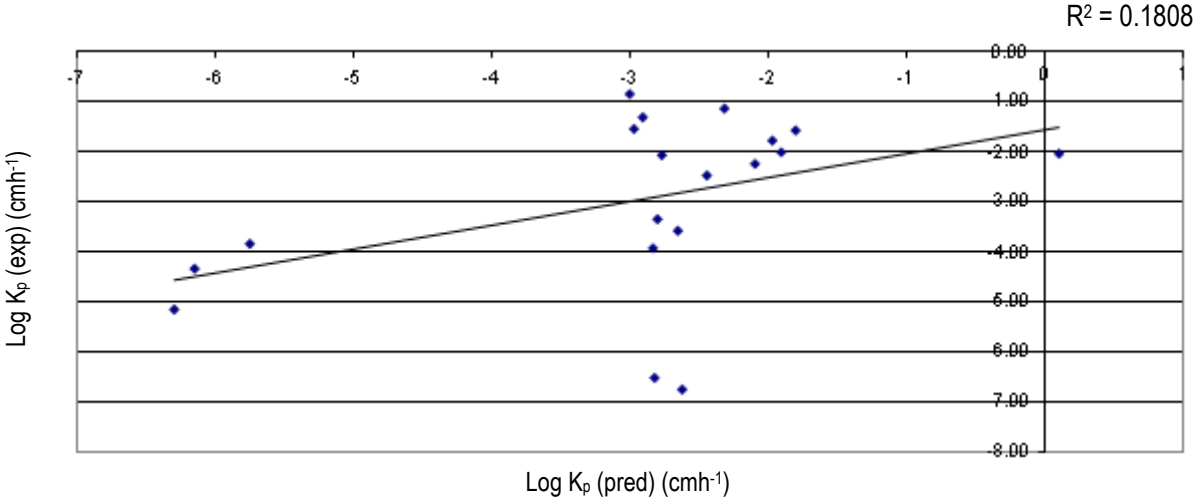
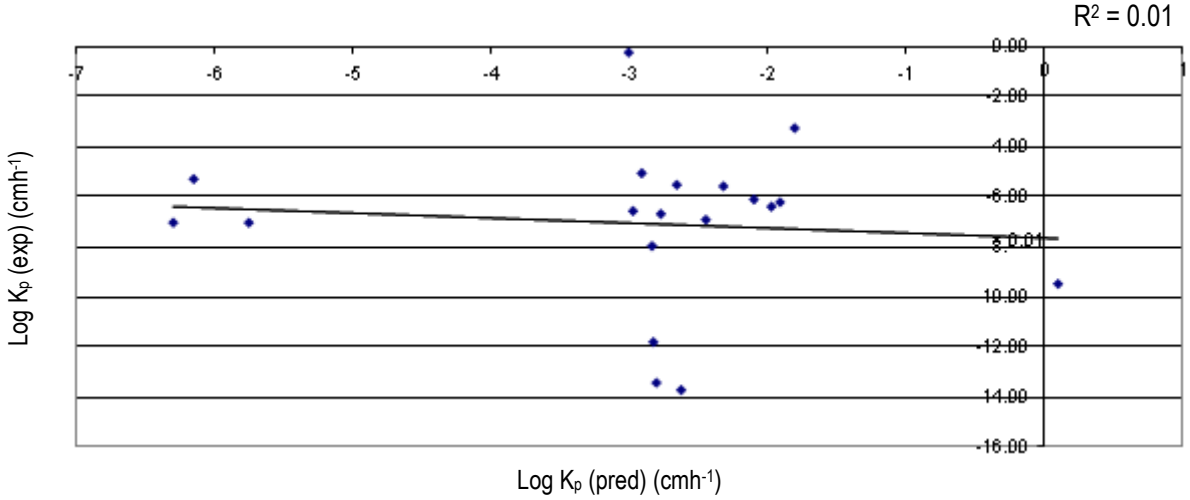


Figure 5. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Barratt.



Appendix 19. Database C. Membrane dataset – Experimental vs predicted K_p values

Membrane dataset – Experimental permeability coefficients and drug properties

No	Name	MW	MPt (^{0}C)	Log P KOWWIN	Log K_p (cmh^{-1})	Journal
1	benzoic acid	194.20	238.00	0.16	-1.70	*Toxicol. Vitro* 6, 303-315
2	caffeine	217.29	106.00	0.84	-2.40	*Toxicol. Vitro* 6, 303-315
3	clotrimazole	165.19	89.00	1.80	-5.87	*Int.J.Pharm.* 215, 51-56
4	DDT	122.10	122.40	1.87	-1.07	*Toxicol. Vitro* 8, 1219-1225
5	flufenamic acid	236.31	61.00	1.99	-6.94	*J.Contr.Rel.* 75, 283-295
6	salicylic acid	138.10	158.00	2.24	0.66	*Int.J.Pharm.* 215, 51-56
7	terbinafine	231.29	119.00	2.90	-2.31	*Int.J.Pharm.* 215, 51-56
8	testosterone	264.37	152.00	3.02	-5.82	*Skin Pharmacol.* 5, 146-153
9	amethocaine	288.40	155.00	3.27	-1.54	*Pred. of Perc.Penetration* 1, 192-198
10	procaine	245.29	105.00	3.39	-2.00	*Pred. of Perc.Penetration* 1, 192-198
11	benzocaine	291.43	132.00	3.60	-6.47	*Pred. of Perc.Penetration* 1, 192-198
12	dibucaine	259.00	116.00	3.89	-1.65	*Pred. of Perc.Penetration* 1 192-198
13	ketocaine	343.47	418.00	4.04	-6.19	*Pred. of Perc.Penetration* 1, 192-198
14	captopril	273.29	127.00	4.38	-1.39	*J.Pharm.Pharmac.* 58, 167-177
15	methyl ester	287.29	138.00	4.87	-1.17	*J.Pharm.Pharmac.* 58, 167-177
16	ethyl ester	281.20	133.00	4.88	-2.51	*J.Pharm.Pharmac.* 58, 167-177
17	propyl ester	266.33	190.00	5.12	-1.54	*J.Pharm.Pharmac.* 58, 167-177
18	butyl ester	301.29	150.00	5.36	-0.91	*J.Pharm.Pharmac.* 58, 167-177
19	pentyl ester	291.40	N/A	5.81	-1.56	*J.Pharm.Pharmac.* 58, 167-177
20	hexyl ester	344.85	148.00	6.26	0.27	*J.Pharm.Pharmac.* 58, 167-177
21	pentachlorophenol	354.50	108.50	6.79	-2.15	*Tox.Sciences* 69 (2007), 295-305

Membrane – Predicted permeability using the Potts and Guy (1992) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Potts & Guy) (cmh^{-1})	Log K_p (exp)- log K_p (Potts & Guy) (cmh^{-1})
1	benzoic acid	-1.07	-2.12	-1.05
2	caffeine	-1.70	-3.77	-2.07
3	clotrimazole	0.27	-0.36	-0.63
4	DDT	-2.15	-0.04	2.11
5	flufenamic acid	-2.51	-0.95	1.56
6	salicylic acid	0.66	-1.95	-2.61
7	terbinafine	-1.56	-0.35	1.21
8	testosterone	-1.54	-2.14	-0.60
9	amethocaine	-5.82	-2.17	3.65
10	procaine	-6.94	-2.73	4.21
11	benzocaine	-5.87	-2.43	3.44
12	dibucaine	-6.19	-1.93	4.26
13	ketocaine	-6.47	-1.92	4.55
14	captopril	-2.40	-3.43	-1.03
15	methyl ester	-2.31	-2.05	0.26
16	ethyl ester	-2.00	-1.79	0.21
17	propyl ester	-1.65	-1.52	0.13
18	butyl ester	-1.39	-1.26	0.13
19	pentyl ester	-1.17	-0.99	0.18
20	hexyl ester	-0.91	-0.73	0.18
21	pentachlorophenol	-1.54	-0.69	0.85

Membrane – Predicted permeability using the revised Robinson (1995) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Robinson) (cmh^{-1})	Log K_p (exp)- log K_p (Robinson) (cmh^{-1})
1	benzoic acid	-1.07	-2.17	-1.10
2	caffeine	-1.70	-3.69	-1.99
3	clotrimazole	0.27	-1.15	-1.42
4	DDT	-2.15	-1.04	1.11
5	flufenamic acid	-2.51	-1.46	1.05
6	salicylic acid	0.66	-2.08	-2.74
7	terbinafine	-1.56	-1.13	0.43
8	testosterone	-1.54	-2.38	-0.84
9	amethocaine	-5.82	-2.40	3.42
10	procaine	-6.94	-2.86	4.08
11	benzocaine	-5.87	-2.53	3.34
12	dibucaine	-6.19	-2.19	4.00
13	ketocaine	-6.47	-2.20	4.27
14	captopril	-2.40	-3.44	-1.04
15	methyl ester	-2.31	-2.29	0.02
16	ethyl ester	-2.00	-2.08	-0.08
17	propyl ester	-1.65	-1.87	-0.22
18	butyl ester	-1.39	-1.67	-0.29
19	pentyl ester	-1.17	-1.49	-0.32
20	hexyl ester	-0.91	-1.33	-0.42
21	pentachlorophenol	-1.54	-1.29	0.24

Membrane – Predicted permeability using the revised Brown and Rossi (1995) model

No	Name	Log K_p (exp) (cmh^{-1})	Log Kp (Brown & Rossi) (cmh^{-1})	Log K_p (exp)- log K_p (Brown & Rossi) (cmh^{-1})
1	benzoic acid	-1.07	-0.76	0.31
2	caffeine	-1.70	-1.96	-0.26
3	clotrimazole	0.27	0.00	-0.27
4	DDT	-2.15	0.00	2.15
5	flufenamic acid	-2.51	-0.01	2.50
6	salicylic acid	0.66	-0.54	-1.20
7	terbinafine	-1.56	0.00	1.56
8	testosterone	-1.54	-0.15	1.39
9	amethocaine	-5.82	-0.22	5.60
10	procaine	-6.94	-0.69	6.25
11	benzocaine	-5.87	-0.80	5.07
12	dibucaine	-6.19	-0.05	6.14
13	ketocaine	-6.47	-0.09	6.38
14	captopril	-2.40	-1.46	0.94
15	methyl ester	-2.31	-0.26	2.05
16	ethyl ester	-2.00	-0.13	1.87
17	propyl ester	-1.65	-0.06	1.59
18	butyl ester	-1.39	-0.03	1.36
19	pentyl ester	-1.17	-0.01	1.16
20	hexyl ester	-0.91	0.00	0.91
21	pentachlorophenol	-1.54	-0.01	1.53

Membrane – Predicted permeability using the Cronin et al. (1999) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Cronin) (cmh^{-1})	Log K_p (exp)- log K_p (Cronin) (cmh^{-1})
1	benzoic acid	-1.07	-2.15	-1.80
2	caffeine	-1.70	-4.21	-2.51
3	clotrimazole	0.27	-1.06	-1.33
4	DDT	-2.15	-0.75	1.40
5	flufenamic acid	-2.51	-1.47	1.04
6	salicylic acid	0.66	-2.03	-2.69
7	terbinafine	-1.56	-0.86	0.70
8	testosterone	-1.54	-2.78	-1.24
9	amethocaine	-5.82	-2.73	3.09
10	procaine	-6.94	-3.23	3.71
11	benzocaine	-5.87	-2.65	3.22
12	dibucaine	-6.19	-2.76	3.43
13	ketocaine	-6.47	-2.56	3.91
14	captopril	-2.40	-3.92	-1.52
15	methyl ester	-2.31	-2.48	-0.17
16	ethyl ester	-2.00	-2.25	-0.25
17	propyl ester	-1.65	-2.01	-0.36
18	butyl ester	-1.39	-1.77	-0.39
19	pentyl ester	-1.17	-1.54	-0.37
20	hexyl ester	-0.91	-1.31	-0.40
21	pentachlorophenol	-1.54	-1.13	0.41

Membrane – Predicted permeability using the Barratt (1995b) model

No	Name	Log K_p (exp) (cmh^{-1})	Log K_p (Barratt) (cmh^{-1})	Log K_p (exp)- log K_p (Barratt) (cmh^{-1})
1	benzoic acid	-1.07	-6.74	-5.67
2	caffeine	-1.70	-13.31	-11.61
3	clotrimazole	0.27	-6.21	-6.48
4	DDT	-2.15	-4.32	-2.17
5	flufenamic acid	-2.51	-6.16	-3.65
6	salicylic acid	0.66	-7.97	-8.63
7	testosterone	-1.54	-8.41	-6.87
8	amethocaine	-5.82	-8.27	-2.45
9	procaine	-6.94	-5.30	1.64
10	benzocaine	-5.87	-5.89	-0.02
11	dibucaine	-6.19	-18.54	-12.35
12	ketocaine	-6.47	-7.27	-0.80
13	captopril	-2.40	-7.83	-5.43
14	methyl ester	-2.31	-6.77	-4.46
15	ethyl ester	-2.00	-5.96	-3.96
16	propyl ester	-1.65	-6.11	-4.46
17	butyl ester	-1.39	-6.26	-4.88
18	pentyl ester	-1.17	-6.42	-5.25
19	hexyl ester	-0.91	-6.62	-5.71
20	pentachlorophenol	-1.54	-8.05	-6.51

Figure 1. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Potts and Guy.

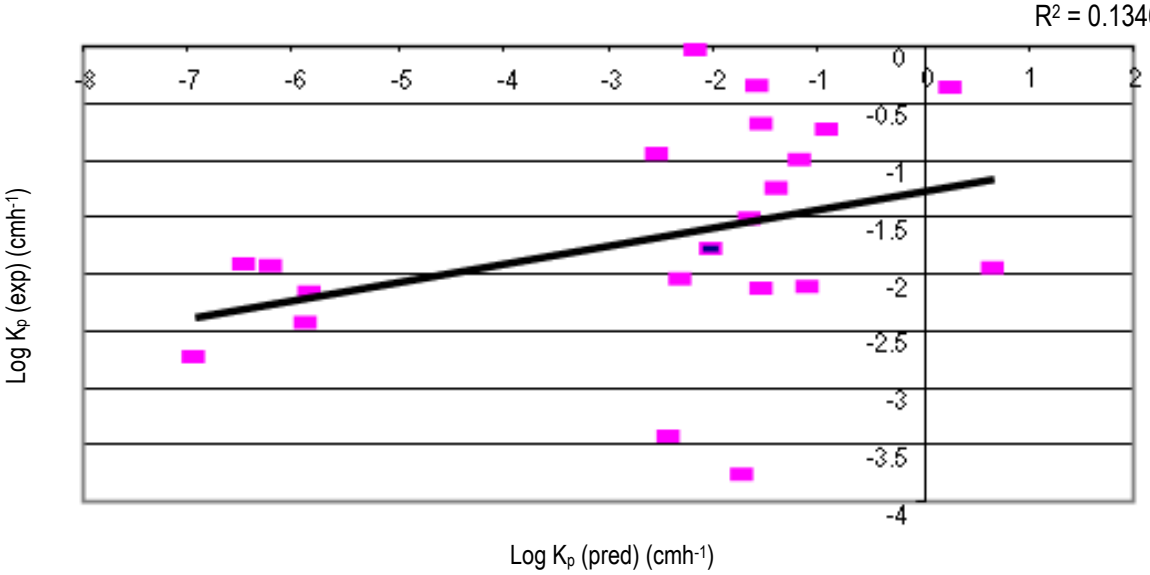


Figure 2. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Robinson.

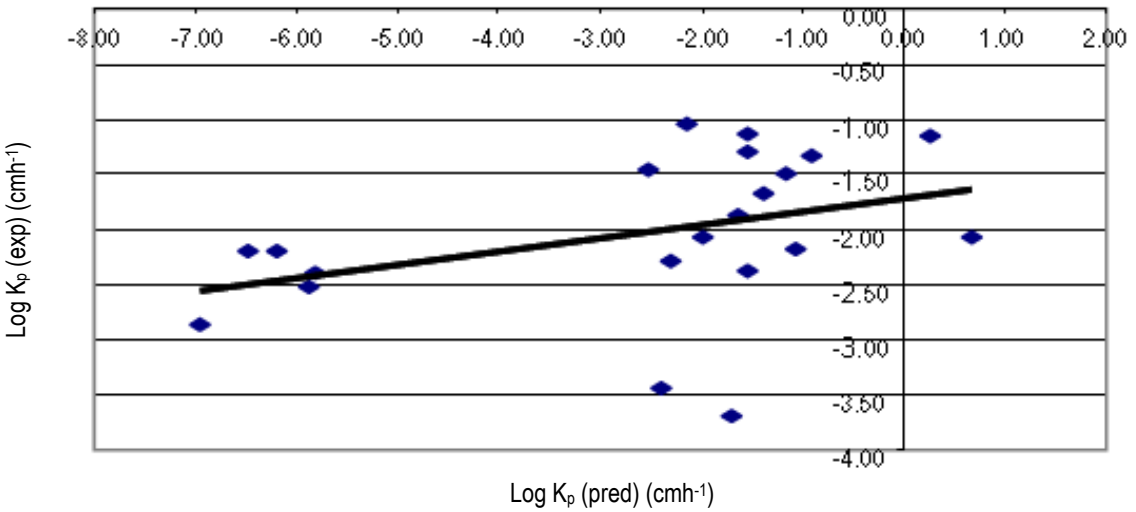


Figure 3. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Brown and Rossi.

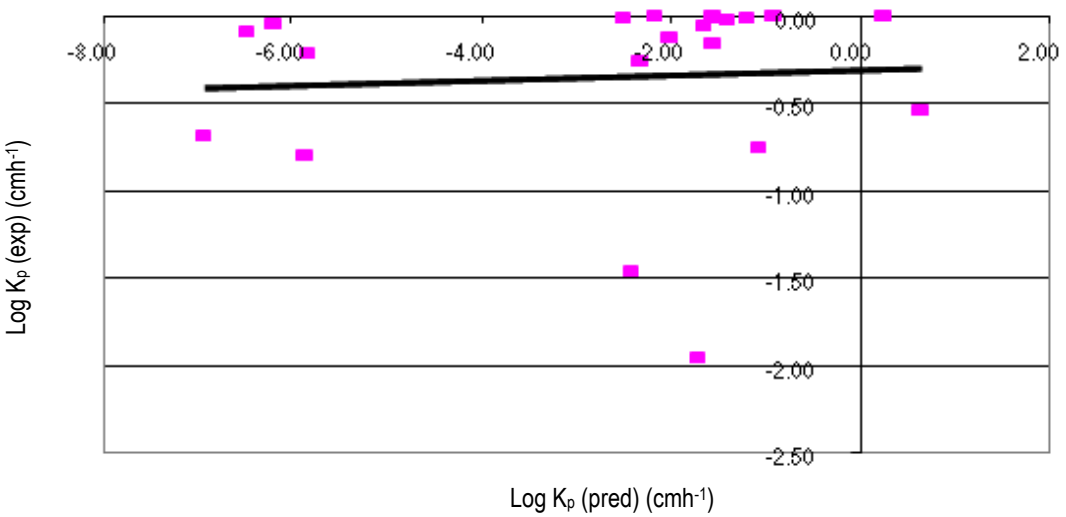


Figure 4. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Cronin.

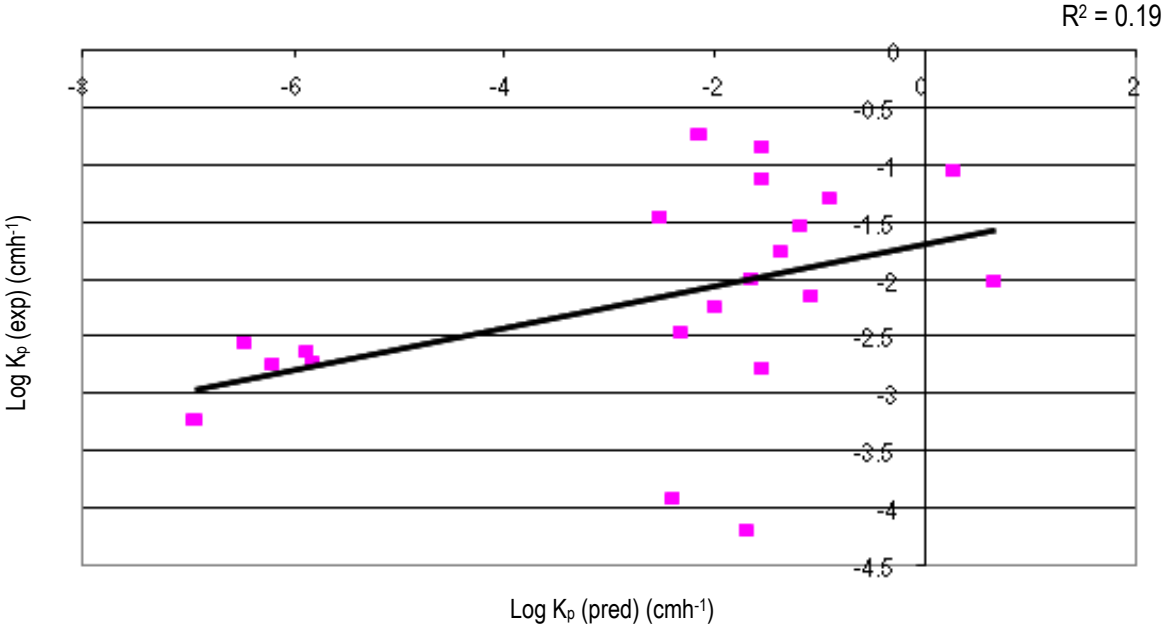
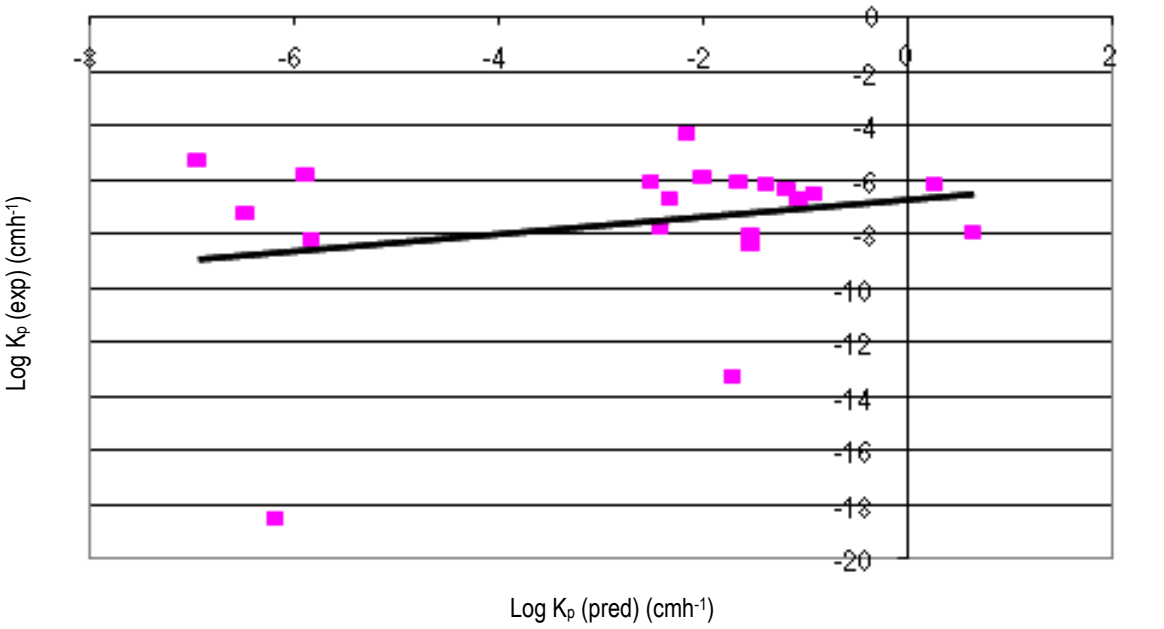


Figure 5. Agreement between log K_p (exp) (cmh^{-1}) and log K_p (cmh^{-1}) predicted by Barratt.



Appendix 20. Consent Form

School of Pharmacy

CONSENT FORM FOR DONATION OF SURGICALLY REMOVED TISSUE

I hereby consent for the tissue that is removed during my surgery to be used by Professor Marc Brown and Drs Gary Moss and Tracy Garnier and their research group for in vitro studies into the development of formulations for the delivery of drugs across and into the skin for the treatment of diseases such as psoriasis, eczema, cancer, acne and other skin infections and Bilharzia.

The donated tissue will be used by Professor Brown in his research and will not be used for any other studies. The donated skin will be stored anonymously in the Topical Drug Delivery Unit at the University of Hertfordshire, UK for a maximum of 2 years after which time it will be incinerated.

More details of the research for which the tissue will be used can be obtained by contacting Professor Marc Brown directly (details given below).

SIGNED _____

DATE _____

Professor Marc Brown
Tel. +44 1707 285187
E-mail M.7.brown@herts.ac.uk

Appendix 21. Receptor fluid (control and spent)

Temozolomide in distilled water

- **Calibration:** A stock solution of 10 mg into 10 ml of distilled water (1000µgml^{-1}) was prepared.

No of stand. sol.	Conc. (µgml^{-1})	Final volume (ml)	Dilution
1	50	10	0.5 ml of stock sol.
2	40	10	0.4 ml of stock sol.
3	30	10	0.3 ml of stock sol.
4	20	10	0.2 ml of stock sol.
5	10	20	0.2 ml of stock sol.
6	5	20	0.1 ml of stock sol.
7	2	10	1ml of stand. sol. 4
8	0.5	10	1 ml of stand. sol 6

- **Stability** of receptor fluid maintained at 37 ^{0}C

Cs = 1736.851 µgml^{-1}, apply 1736.851 µgml^{-1} and if the total volume of receiver fluid equals 2 ml

For 1.01% absorption [%abs = (0.04255 x2) x 100/1.736851] Conc. = 8.811 µgml^{-1}

Sample 1, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.02 ml (20µg/0.02ml) of stock solution (1) into 2.25 ml of receiver fluid
Sample 2, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.02 ml (20µg/0.02ml) of stock solution (1) into 2.25 ml of receiver fluid
Sample 3, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.02 ml (20µg/0.02ml) of stock solution (1) into 2.25 ml of receiver fluid

For 2.5 % absorption [%abs = (0.021739x2) x 100/1.736851] Conc. = 21.739 µgml^{-1}

Sample 4, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml of receiver fluid
Sample 5, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml of receiver fluid
Sample 6, 0.75 ml per withdrawal -8h, 24h, and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml of receiver fluid

LOD µgml^{-1}	LOQ µgml^{-1}
1.54635	4.685908

Procaine diluted in PBS : water (20:80)

- **Calibration:** A stock solution of 100 mg into 100 ml of PBS : water (20:80) (1000µgml^{-1}) was prepared.

No of stand. sol.	Conc. (µgml^{-1})	Final volume (ml)	Dilution
1	50	10	0.5 ml of stock sol.
2	40	10	0.4 ml of stock sol.
3	30	10	0.3 ml of stock sol.
4	20	10	0.2 ml of stock sol.
5	10	20	0.2 ml of stock sol.
6	5	20	0.1 ml of stock sol.
7	2	10	1 ml of stand. sol. 4
8	0.5	10	1 ml of stand. sol 6

- **Stability** of receptor fluid maintained at 37 ^{0}C.

Cs = 6644341.09 µgml^{-1}, apply 6644341.09 µgml^{-1} and if the total volume of receiver fluid equals 2 ml

For 0.0013 % absorption [%abs= (0.04255 x2) x 100/6644.34109] Conc. = 42.55 µgml^{-1}

Sample 1, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.1 ml (100µg/0.1ml) of stock solution (1) into 2.25 ml of receiver fluid
Sample 2, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.1 ml (100µg/0.1ml) of stock solution (1) into 2.25 ml of receiver fluid
Sample 3, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.1 ml (100µg/0.1ml) of stock solution (1) into 2.25 ml of receiver fluid

For 0.00065 % absorption [%abs= (0.021739x2) x 100/6644.34109] Conc. = 21.739 µgml^{-1}

Sample 4, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml of receiver fluid
Sample 5, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml of receiver fluid
Sample 6, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml of receiver fluid

LOD µgml^{-1}	LOQ µgml^{-1}
0.674311	2.043365

Furosemide diluted in 40% PEG 400 in water

- **Calibration:** A stock solution of 50 mg into 50 ml of 40% PEG 400 (1000µgml^{-1}) was prepared.

No of stand. sol.	Conc. (µgml^{-1})	Final volume (ml)	Dilution
1	50	10	0.5 ml of stock sol.
2	40	10	0.4 ml of stock sol.
3	30	10	0.3 ml of stock sol.
4	20	10	0.2 ml of stock sol.
5	10	20	0.2 ml of stock sol.
6	5	20	0.1 ml of stock sol.
7	2	10	1 ml of stand. sol. 4
8	0.5	10	1 ml of stand. sol. 6

- **Stability** of receptor fluid maintained at 37 ^{0}C

Cs =13196.56561 µgml^{-1}, apply 13196.56561 µgml^{-1} and if the total volume of receiver fluid equals 2 ml

For 0.645 % absorption [% abs= (0.04255 x2) x 100/13.197] Conc. = 42.55 µgml^{-1}

Sample 1, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.1 ml (100µg/0.1ml) of stock solution (1) into 2.25 ml of receiver fluid
Sample 2, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.1 ml (100µg/0.1ml) of stock solution (1) into 2.25 ml of receiver fluid
Sample 3, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.1 ml (100µg/0.1ml) of stock solution (1) into 2.25 ml of receiver fluid

For 0.33 % absorption [% abs= (0.021739x2) x 100/13.197] Conc. = 21.739 µgml^{-1}

Sample 4, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml of receiver fluid
Sample 5, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml of receiver fluid
Sample 6, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml of receiver fluid

LOD µgml^{-1}	LOQ µgml^{-1}
0.449303	1.361525

Paracetamol diluted in PBS

Calibration: A stock solution of 100 mg into 100 ml of PBS (1000µgml^{-1}) was prepared.

No of stand. sol.	Conc. (µgml^{-1})	Final volume (ml)	Dilution
1	50	10	0.5 ml of stock sol.
2	40	10	0.4 ml of stock sol.
3	30	10	0.3 ml of stock sol.
4	20	10	0.2 ml of stock sol.
5	10	20	0.2 ml of stock sol.
6	5	20	0.1 ml of stock sol.
7	2	10	1 ml of stand. sol. 4
8	0.5	10	1 ml of stand. sol. 6

- **Stability** of receptor fluid maintained at 37 ^{0}C

Cs = 419.1961 µgml^{-1}, apply 419.1961 µgml^{-1} and if the total volume of receiver fluid equals 2 ml

For 4.20% absorption [% abs= (0.04255 x2) x 100/0.41920] Conc. = 8.81 µgml^{-1}

Sample 1, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.02 ml (20µg/0.02ml) of stock solution (1) into 2.25 ml of receiver fluid
Sample 2, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.02 ml (20µg/0.02ml) of stock solution (1) into 2.25 ml of receiver fluid
Sample 3, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.02 ml (20µg/0.02ml) of stock solution (1) into 2.25 ml of receiver fluid

For 3.5% absorption [% abs= (0.04255 x2) x 100/0.41920] Conc. = 7.35 µgml^{-1}

Sample 1, 0.9 ml per withdrawal -8h, 24h and 48h:
Apply 0.02 ml (20µg/0.02ml) of stock solution (1) into 2.7 ml of receiver fluid
Sample 2, 0.9 ml per withdrawal -8h, 24h and 48h:
Apply 0.02 ml (20µg/0.02ml) of stock solution (1) into 2.7 ml of receiver fluid
Sample 3, 0.9 ml per withdrawal -8h, 24h and 48h:
Apply 0.02 ml (20µg/0.02ml) of stock solution (1) into 2.7 ml of receiver fluid

LOD µgml^{-1}	LOQ µgml^{-1}
0.062809	0.19033

Ibuprofen diluted in PBS (pH 7.4)

- **Calibration:** Stock solution of 50mg into 50 ml of PBS (1000µgml^{-1}) was prepared.

No of stand. sol.	Conc. (µgml^{-1})	Final volume (ml)	Dilution
1	50	10	0.5 ml of stock sol.
2	40	10	0.4 ml of stock sol.
3	30	10	0.3 ml of stock sol.
4	20	10	0.2 ml of stock sol.
5	10	20	0.2 ml of stock sol.
6	5	20	0.1 ml of stock sol.
7	2	10	1 ml of stand. sol. 4
8	0.5	10	1 ml of stand. sol. 6

- **Stability** of receptor fluid maintained at 37 ^{0}C

Cs = 24644.09439 µgml^{-1}, apply 24644.09439µgml^{-1} and if the total volume of receiver fluid equals 2 ml

For 0.34 % absorption [% abs= (0.04255 x2) x 100/24.644] Conc. = 42.55 µgml^{-1}

Sample 1, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.1 ml (100µg/0.1ml) of stock solution (1) into 2.25 ml of receiver fluid
Sample 2, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.1 ml (100µg/0.1ml) of stock solution (1) into 2.25 ml of receiver fluid.
Sample 3, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.1 ml (100µg/0.1ml) of stock solution (1) into 2.25 ml of receiver fluid

For 0.176 % absorption [% abs= (0.021739x2) x 100/24.644] Conc. = 21.739 µgml^{-1}

Sample 4, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml of receiver fluid
Sample 5, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml of receiver fluid
Sample 6, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml of receiver fluid

LOD µgml^{-1}	LOQ µgml^{-1}
0.531196	1.609684

Ibuprofen diluted in solvent (pH 4.2)

- Total amount available in stock 1g
- **Calibration:** prepare **stock solution (1)** of 10 mg into 10 ml of solvent (1000µgml^{-1}). 0.1 mg were added into 10 ml (100 µgml^{-1})

No of stand. sol.	Conc. (µgml^{-1})	Final volume (ml)	Dilution
1	50	10	0.5 ml of stock sol.
2	40	10	0.4 ml of stock sol.
3	30	10	0.3 ml of stock sol.
4	20	10	0.2 ml of stock sol.
5	10	20	0.2 ml of stock sol.
6	5	20	0.1 ml of stock sol.
7	2	10	1 ml of stand. sol. 4
8	0.5	10	1 ml of stand. sol. 6

- **Stability:** Receptor fluid in contact with human skin tissue (epidermal sheet) at 37 ^{0}C.

Cs = 644.45 µgml^{-1}= 0.6445 mg/ml, apply 500 µgml^{-1} and if the total volume of receiver fluid equals 2 ml

For 6.75 % absorption [% abs= (0.021739 x 2) x 100/0.6445] Conc. = 21.739 µgml^{-1}

Sample 1, 0.75 ml per withdrawal -8hrs, 24hrs and 48hrs:
Apply 0.05 ml (5µg/0.05ml) of stock solution (1) into 2.25 ml (receiver fluid).
Sample 2, 0.75 ml per withdrawal -8hrs, 24hrs and 48hrs:
Apply 0.05 ml (5µg/0.05ml) of stock solution (1) into 2.25 ml (receiver fluid).
Sample 3, 0.75 ml per withdrawal -8hrs, 24hrs and 48hrs:
Apply 0.05 ml (5µg/0.05ml) of stock solution (1) into 2.25 ml (receiver fluid).

For 1.32 % absorption [% abs= (0.004255 x 2) x 100/0.6445] Conc. = 4.255 µgml^{-1}

Sample 4, 0.75 ml per withdrawal -8hrs, 24hrs and 48hrs:
Apply 0.01 ml (1 µg/0.01 ml) of stock solution (1) into 2.34 ml (receiver fluid).
Sample 5, 0.75 ml per withdrawal -8hrs, 24hrs and 48hrs:

Apply 0.01 ml (1 µg/0.01 ml) of stock solution (1) into 2.34 ml (receiver fluid).
Sample 6, 0.75 ml per withdrawal -8hrs, 24hrs and 48hrs:
Apply 0.01 ml (1 µg/0.01 ml) of stock solution (1) into 2.34 ml (receiver fluid).

Set up of 2 Franz cell (10ml) with solvent (pH 4.2)

DL	QL
1.163762098	3.526551812

Ibuprofen diluted in solvent (pH 2.4)

- Total amount available in stock 1g
- **Calibration:** prepare **stock solution (1)** of 10 mg into 10 ml of PBS (1000µgml^{-1}). 0.1 mg into 10 ml (100 µgml^{-1})

No of stand. sol.	Conc. (µgml^{-1})	Final volume (ml)	Dilution
1	50	10	0.5 ml of stock sol.
2	40	10	0.4 ml of stock sol.
3	30	10	0.3 ml of stock sol.
4	20	10	0.2 ml of stock sol.
5	10	20	0.2 ml of stock sol.
6	5	20	0.1 ml of stock sol.
7	2	10	1ml of stand. sol. 4
8	0.5	10	1 ml of stand.sol 6

- **Stability:** Receptor Fluid in contact with human skin tissue (epidermal sheet) at 37 ^{0}C.

Cs = 59.04 µgml^{-1}= 0.05904 mg/ml, apply10000 µgml^{-1} and if the total vol. of receiver fluid equals 2 ml

For 7.36% absorption [% abs= (0.0021739 x 2) x 100/0.05904] Conc. = 2.1739 µgml^{-1}

Sample 1, 0.75 ml per withdrawal -8hrs, 24hrs and 48hrs:
Apply 0.01 ml (1µg/0.01ml) of stock solution (1) into 4.59 ml (receiver fluid).
Sample 2, 0.75 ml per withdrawal -8hrs, 24hrs and 48hrs:
Apply 0.01 ml (1µg/0.01ml) of stock solution (1) into 4.59 ml (receiver fluid).
Sample 3, 0.75 ml per withdrawal -8hrs, 24hrs and 48hrs:
Apply 0.01 ml (1µg/0.01ml) of stock solution (1) into 4.59 ml (receiver fluid).

Set up of 4 Franz cell (10ml) with solvent (pH 2.6)

DL	QL
1.163762098	3.526551812

Spent Receiver Fluid

Temozolomide in distilled water

- **Calibration:** A stock solution of 10mg into 10 ml of distilled water (1000µgml^{-1}) was prepared.

No of stand. sol.	Conc. (µgml^{-1})	Final volume (ml)	Dilution
1	50	10	0.5 ml of stock sol.
2	40	10	0.4 ml of stock sol.
3	30	10	0.3 ml of stock sol.
4	20	10	0.2 ml of stock sol.
5	10	20	0.2 ml of stock sol.
6	5	20	0.1 ml of stock sol.

No of stand. sol.	Conc. (µgml^{-1})	Final volume (ml)	Dilution
7	2	10	1 ml of stand. sol. 4
8	0.5	10	1 ml of stand. sol. 6

- **Stability** of receptor fluid maintained at 37 ^{0}C.

Cs = 1736.851 µgml^{-1}, apply 1736.851 µgml^{-1} and if the total volume of receiver fluid equals 2 ml

For 1.01% absorption [% abs= (0.04255 x 2) x 100/1.736851] Conc. = 8.811 µgml^{-1}

Sample 1, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.02 ml (20µg/0.02ml) of stock solution (1) into 2.25 ml (spent receiver fluid).
Sample 2, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.02 ml (20µg/0.02ml) of stock solution (1) into 2.25 ml (spent receiver fluid).
Sample 3, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.02 ml (20µg/0.02ml) of stock solution (1) into 2.25 ml (spent receiver fluid).

For 2.5 % absorption [% abs= (0.021739 x 2)x 100/1.736851] Conc. = 21.739 µgml^{-1}

Sample 4, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml (spent receiver fluid).
Sample 5, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml (spent receiver fluid).
Sample 6, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml (spent receiver fluid).

LOD µgml^{-1}	LOQ µgml^{-1}
1.54635	4.685908

Procaine diluted in PBS : water (20:80)

- **Calibration:** A stock solution of 100 mg into 100 ml of PBSb : water (20:80) (1000µgml^{-1}) was prepared.

No of stand. sol.	Conc. (µgml^{-1})	Final volume (ml)	Dilution
1	50	10	0.5 ml of stock sol.
2	40	10	0.4 ml of stock sol.
3	30	10	0.3 ml of stock sol.
4	20	10	0.2 ml of stock sol.
5	10	20	0.2 ml of stock sol.
6	5	20	0.1 ml of stock sol.
7	2	10	1 ml of stand. sol. 4
8	0.5	10	1 ml of stand. sol. 6

- **Stability** of receptor fluid maintained at 37 ^{0}C.

Cs = 6644341.09 µgml^{-1}, apply 6644341.09 µgml^{-1} and if the total volume of receiver fluid equals 2 ml

For 0.0013 % absorption [% abs= (0.04255 x 2) x 100/6644.34109] Conc. = 42.55 µgml^{-1}

Sample 1, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.1 ml (100µg/0.1ml) of stock solution (1) into 2.25 ml (spent receiver fluid).
Sample 2, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.1 ml (100µg/0.1ml) of stock solution (1) into 2.25 ml (spent receiver fluid).
Sample 3, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.1 ml (100µg/0.1ml) of stock solution (1) into 2.25 ml (spent receiver fluid).

For 0.00065 % absorption [% abs= (0.021739 x 2) x 100/6644.34109] Conc. = 21.739 µgml^{-1}

Sample 4, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml (spent receiver fluid).
Sample 5, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml (spent receiver fluid).
Sample 6, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml (spent receiver fluid).

LOD µgml^{-1}	LOQ µgml^{-1}
0.674311	2.043365

Furosemide diluted in 40% PEG 400 in water

Calibration: A stock solution of 50 mg into 50 ml of 40% PEG 400 (1000µgml^{-1}) was prepared.

No of stand. sol.	Conc. (µgml^{-1})	Final volume (ml)	Dilution
1	50	10	0.5 ml of stock sol.
2	40	10	0.4 ml of stock sol.
3	30	10	0.3 ml of stock sol.
4	20	10	0.2 ml of stock sol.
5	10	20	0.2 ml of stock sol.
6	5	20	0.1 ml of stock sol.
7	2	10	1 ml of stand. sol. 4
8	0.5	10	1 ml of stand. sol. 6

- **Stability** of receptor fluid maintained at 37 ^{0}C

Cs =13196.56561 µgml^{-1}, apply 13196.56561 µgml^{-1} and if the total volume of receiver fluid equals 2 ml

For 0.645 % absorption [% abs= (0.04255 x 2) x 100/13.197] Conc. = 42.55 µgml^{-1}

Sample 1, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.1 ml (100µg/0.1ml) of stock solution (1) into 2.25 ml (spent receiver fluid).
Sample 2, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.1 ml (100µg/0.1ml) of stock solution (1) into 2.25 ml (spent receiver fluid).
Sample 3, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.1 ml (100µg/0.1ml) of stock solution (1) into 2.25 ml (spent receiver fluid).

For 0.33 % absorption [% abs= (0.021739x2) x 100/13.197] Conc. = 21.739 µgml^{-1}

Sample 4, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml (spent receiver fluid).
Sample 5, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml (spent receiver fluid).
Sample 6, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml (spent receiver fluid).

LOD µgml^{-1}	LOQ µgml^{-1}
0.449303	1.361525

Paracetamol diluted in PBS

Calibration: A stock solution of 100 mg into 100 ml of PBS (1000µgml^{-1}) was prepared.

No of stand. sol.	Conc. (µgml^{-1})	Final volume (ml)	Dilution
1	50	10	0.5 ml of stock sol.
2	40	10	0.4 ml of stock sol.
3	30	10	0.3 ml of stock sol.
4	20	10	0.2 ml of stock sol.
5	10	20	0.2 ml of stock sol.
6	5	20	0.1 ml of stock sol.
7	2	10	1 ml of stand. sol. 4
8	0.5	10	1 ml of stand. sol. 6

- **Stability** of receptor fluid maintained at 37 ^{0}C

Cs = 419.1961 µgml^{-1}, apply 419.1961 µgml^{-1} and if the total vol. of receiver fluid equals 2 ml

For 4.20% absorption [% abs= (0.04255 x 2) x 100/0.41920] Conc. = 8.81 µgml^{-1}

Sample 1, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.02 ml (20µg/0.02ml) of stock solution (1) into 2.25 ml (spent receiver fluid).
Sample 2, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.02 ml (20µg/0.02ml) of stock solution (1) into 2.25 ml (spent receiver fluid).
Sample 3, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.02 ml (20µg/0.02ml) of stock solution (1) into 2.25 ml (spent receiver fluid).

For 3.5% absorption [% abs= (0.04255 x 2) x 100/0.41920] Conc. = 7.35 µgml^{-1}

Sample 1, 0.9 ml per withdrawal -8h, 24h and 48h:
Apply 0.02 ml (20µg/0.02ml) of stock solution (1) into 2.7 ml (spent receiver fluid).
Sample 2, 0.9 ml per withdrawal -8h, 24h and 48h:
Apply 0.02 ml (20µg/0.02ml) of stock solution (1) into 2.7 ml (spent receiver fluid).
Sample 3, 0.9 ml per withdrawal -8h, 24h and 48h:
Apply 0.02 ml (20µg/0.02ml) of stock solution (1) into 2.7 ml (spent receiver fluid).

LOD µgml^{-1}	LOQ µgml^{-1}
0.062809	0.19033

Ibuprofen diluted in PBS (pH 7.4)

- **Calibration:** Stock solution of 50mg into 50 ml of PBS (1000µgml^{-1}) was prepared.

No of stand. sol.	Conc. (µgml^{-1})	Final volume (ml)	Dilution
1	50	10	0.5 ml of stock sol.
2	40	10	0.4 ml of stock sol.
3	30	10	0.3 ml of stock sol.
4	20	10	0.2 ml of stock sol.
5	10	20	0.2 ml of stock sol.
6	5	20	0.1 ml of stock sol.
7	2	10	1 ml of stand. sol. 4
8	0.5	10	1 ml of stand. sol. 6

- **Stability** of receptor fluid maintained at 37 ^{0}C

Cs = 24644.09439 µgml^{-1}, apply 24644.09439µgml^{-1} and if the total volume of receiver fluid equals 2 ml

For 0.34 % absorption [% abs= (0.04255 x 2) x 100/24.644] Conc. = 42.55 µgml^{-1}

Sample 1, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.1 ml (100µg/0.1 ml) of stock solution (1) into 2.25 ml (spent receiver fluid)

Sample 2, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.1 ml (100µg/0.1 ml) of stock solution (1) into 2.25 ml (spent receiver fluid)
Sample 3, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.1 ml (100µg/0.1 ml) of stock solution (1) into 2.25 ml (spent receiver fluid)

For 0.176 % absorption [% abs= (0.021739 x 2) x 100/24.644] Conc. = 21.739 µgml^{-1}

Sample 4, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml (spent receiver fluid)
Sample 5, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml (spent receiver fluid)
Sample 6, 0.75 ml per withdrawal -8h, 24h and 48h:
Apply 0.05 ml (50µg/0.05ml) of stock solution (1) into 2.25 ml (spent receiver fluid)

LOD µgml^{-1}	LOQ µgml^{-1}
0.531196	1.609684

Ibuprofen diluted in solvent (pH 4.2)

- Total amount available in stock 1g
- **Calibration:** prepare **stock solution (1)** of 10 mg into 10 ml of solvent (1000µgml^{-1}). 0.1 mg were added into 10 ml (100 µgml^{-1}).

No of stand. sol.	Conc. (µgml^{-1})	Final volume (ml)	Dilution
1	50	10	0.5 ml of stock sol.
2	40	10	0.4 ml of stock sol.
3	30	10	0.3 ml of stock sol.
4	20	10	0.2 ml of stock sol.
5	10	20	0.2 ml of stock sol.
6	5	20	0.1 ml of stock sol.
7	2	10	1 ml of stand. sol. 4
8	0.5	10	1 ml of stand. sol. 6

- **Stability:** Receptor fluid in contact with human skin tissue (epidermal sheet) at 37 ^{0}C.

Cs = 644.45 µgml^{-1}= 0.6445 mg/ml, apply 500 µgml^{-1} and if the total volume of receiver fluid equals 2 ml

For 6.75 % absorption [% abs= (0.021739 x 2) x 100/0.6445] Conc. = 21.739 µgml^{-1}

Sample 1, 0.75 ml per withdrawal -8hrs, 24hrs and 48hrs:
Apply 0.05 ml (5µg/0.05ml) of stock solution (1) into 2.25 ml (spent receiver fluid).
Sample 2, 0.75 ml per withdrawal -8hrs, 24hrs and 48hrs:
Apply 0.05 ml (5µg/0.05ml) of stock solution (1) into 2.25 ml (spent receiver fluid).
Sample 3, 0.75 ml per withdrawal -8hrs, 24hrs and 48hrs:
Apply 0.05 ml (5µg/0.05ml) of stock solution (1) into 2.25 ml (spent receiver fluid).

For 1.32 % absorption [% abs= (0.004255 x 2) x 100/0.6445] Conc. = 4.255 µgml^{-1}

Sample 4, 0.75 ml per withdrawal -8hrs, 24hrs and 48hrs:
Apply 0.01 ml (1 µg/0.01 ml) of stock solution (1) into 2.34 ml (spent receiver fluid).
Sample 5, 0.75 ml per withdrawal -8hrs, 24hrs and 48hrs:
Apply 0.01 ml (1 µg/0.01 ml) of stock solution (1) into 2.34 ml (spent receiver fluid).
Sample 6, 0.75 ml per withdrawal -8hrs, 24hrs and 48hrs:
Apply 0.01 ml (1 µg/0.01 ml) of stock solution (1) into 2.34 ml (spent receiver fluid).

- Total amount available in stock 1g.
- **Calibration:** prepare **stock solution (1)** of 10 mg into 10 ml of PBS (1000µgml^{-1}). 0.1 mg into 10 ml (100 µgml^{-1})

No of stand. sol.	Conc. (µgml^{-1})	Final volume (ml)	Dilution
1	50	10	0.5 ml of stock sol.
2	40	10	0.4 ml of stock sol.
3	30	10	0.3 ml of stock sol.
4	20	10	0.2 ml of stock sol.
5	10	20	0.2 ml of stock sol.
6	5	20	0.1 ml of stock sol.
7	2	10	1 ml of stand. sol. 4
8	0.5	10	1 ml of stand. sol. 6

- **Stability:** Receptor fluid in contact with human skin tissue (epidermal sheet) at 37 ^{0}C.

Cs = 59.04 µgml^{-1}= 0.05904 mg/ml, apply10000 µgml^{-1} and if the total volume of receiver fluid equals 2 ml

For 7.36% absorption [% abs= (0.0021739 x 2) x 100/0.05904] Conc. = 2.1739 µgml^{-1}

Sample 1, 0.75 ml per withdrawal -8hrs, 24hrs and 48hrs:
Apply 0.01 ml (1µg/0.01ml) of stock solution (1) into 4.59 ml (spent receiver fluid).
Sample 2, 0.75 ml per withdrawal -8hrs, 24hrs and 48hrs:
Apply 0.01 ml (1µg/0.01ml) of stock solution (1) into 4.59 ml (spent receiver fluid).
Sample 3, 0.75 ml per withdrawal -8hrs, 24hrs and 48hrs:
Apply 0.01 ml (1µg/0.01ml) of stock solution (1) into 4.59 ml (spent receiver fluid).

DL	QL
1.163762098	3.526551812

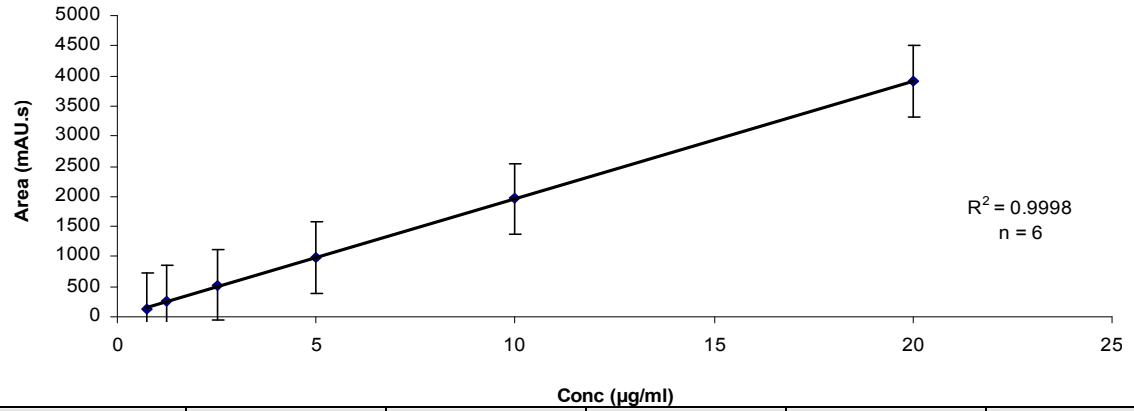
Appendix 22. Log D data (Avdeef 2003)

Name	Log D	MW	SP $(cal/cm^3)^{1/2}$	Log P KOWWIN	Ha	Hd	K_p (cmh^{-1})	Log K_p (cmh^{-1})
atenolol	-2.01	266.30	12.49	-0.03	4	3	0.00005	-4.30
benzoic acid	-1.25	122.10	11.94	1.87	1	1	0.00133	-2.88
betamethasone	2.10	392.45	12.37	2.02	6	3	0.000002	-5.70
caffeine	-0.07	194.20	32.83	0.16	4	0	0.00021	-3.68
celiprolol	-0.16	379.50	11.51	1.93	5	3	0.00059	-3.23
cimetidine	0.34	252.34	12.86	0.40	6	3	0.000038	-4.42
clotrimazole	5.20	344.85	11.17	6.26	2	0	0.002	-2.70
codeine	0.22	299.40	12.09	1.28	4	1	0.000049	-4.31
coumarin	1.44	146.15	11.91	1.51	1	0	0.0091	-2.04
dichlofenac	1.30	296.16	11.13	4.02	2	2	0.001	-3.00
doxycycline HCL	0.23	444.44	16.55	-1.36	9	6	0.00000477	-5.32
ethinyl estradiol	3.42	296.40	12.04	4.00	2	1	0.0000374	-4.43
famotidine	-0.62	337.43	16.08	-0.64	5	4	0.000016	-4.79
flufenamic acid	2.45	281.20	10.96	4.88	5	2	0.0005499	-3.26
griseofulvin	2.18	352.77	10.44	1.92	6	0	0.00194	-2.71
hydrocortisone	2.19	362.50	12.75	1.61	5	3	0.000158	-3.80
ketoprofen	-0.11	254.29	11.75	3.12	2	1	0.00062	-3.21
lidocaine	1.72	234.34	8.78	1.66	2	1	0.0106	-1.97
methotrexate	-2.93	454.45	15.05	-1.28	10	5	0.000113	-3.95
metoprolol	-0.24	267.40	10.39	1.69	4	2	0.00083	-3.08
morphine	-0.06	285.30	13.68	0.72	4	2	0.0000093	-5.03
naproxene	0.09	230.30	11.42	3.10	2	1	0.00288	-2.54
nicotine	0.45	162.30	11.25	1.00	2	0	0.0103	-1.99
oxprenolol	0.18	265.40	10.52	1.83	4	2	0.00154	-2.81
phenol	1.48	94.11	12.33	1.51	1	1	0.00822	-2.09
pirimicarb	1.71	238.29	11.05	1.40	4	0	0.0027	-2.57
prednisolone	1.83	360.44	12.96	1.49	5	3	0.0000235	-4.63
prednisone	1.44	358.44	12.71	1.46	5	2	0.0000246	-4.61
progesterone	3.48	314.50	10.05	3.67	2	0	0.03	-1.52
propranolol	1.41	295.30	11.13	2.60	3	2	0.00178	-2.75
ranitidine	-0.53	314.10	11.41	0.29	5	2	0.0000887	-4.05
salicylic acid	-1.68	138.10	14.39	2.24	2	2	0.0131	-1.89
ibuprofen	1.44	206.30	10.21	3.97	1	1	0.0363	-1.44

Appendix 23. Calibration curves

A. Examples of calibration curves

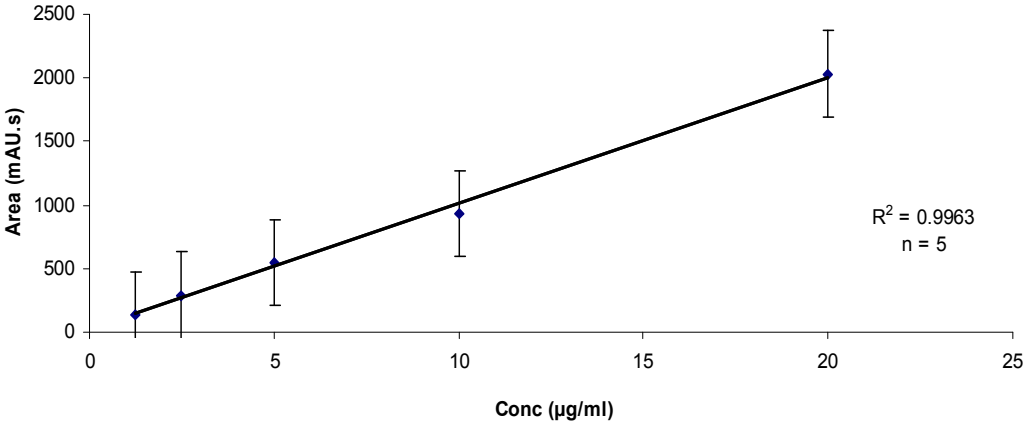
1. Furosemide in 10% PEG400.



Sample	Conc (µgml-1)	Area (mAU.s)	Area (mAU.s)	Area (mAU.s)	Average Area (mAU.s)
1	40	8010.23	7990.54	7999.99	8000.39
2	20	3940.45	3886.31	3886.41	3913.38
3	10	1961.71	1958.75	1959.91	1960.12
4	5	981.69	983.94	989.18	984.94
5	2.5	520.23	536.74	533.10	530.02
6	1.25	262.90	265.58	265.71	264.73
7	0.75	133.43	132.77	133.16	133.12
8	0.375	66.78	64.36	64.43	65.19

STEYX	SLOPE	DL	QL
20.19	194.96	0.34	1.04

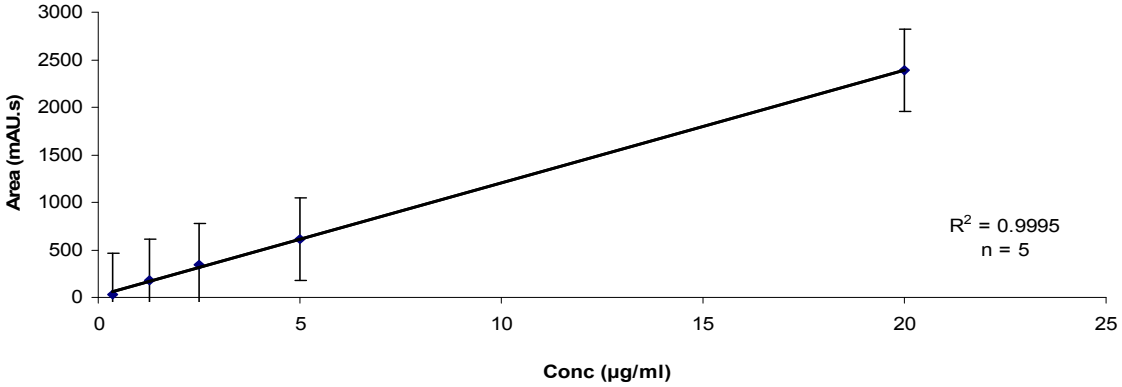
2. Procaine HCl in PBS.



Sample	Conc (µgml-1)	Area (mAU.s)	Area (mAU.s)	Area (mAU.s)	Average Area (mAU.s)
1	40	3639.77	3541.84	3555.75	3579.12
2	20	2366.50	1770.92	1955.71	2031.04
3	10	933.91	934.99	934.99	934.63
4	5	580.34	534.17	534.17	549.56
5	2.5	298.01	303.24	274.51	291.92
6	1.25	137.95	141.73	138.68	139.45
7	0.75	187.92	188.43	187.34	187.90
8	0.375	93.96	92.33	92.10	92.80

STEYX	SLOPE	DL	QL
53.01	99.07	1.76	5.35

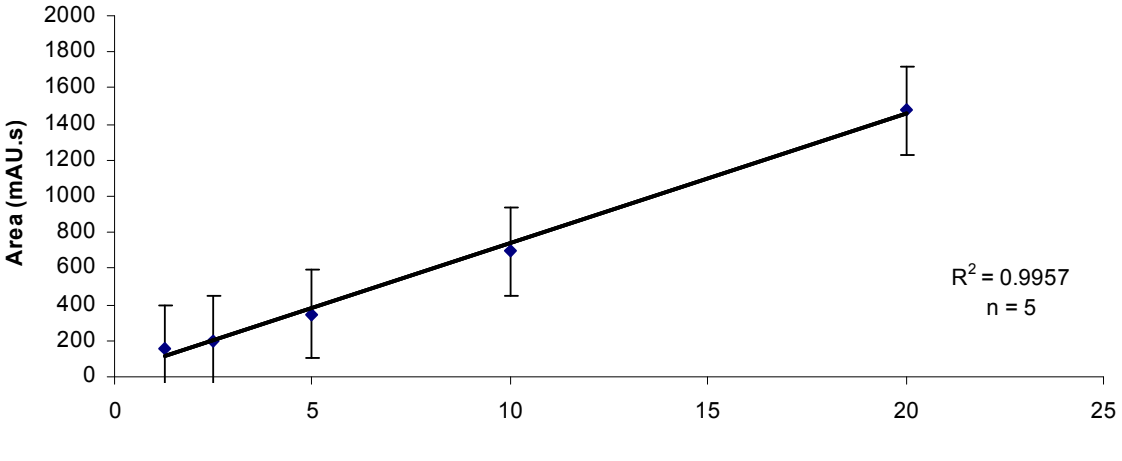
3. Procaine in PBS : water (20:80).



Sample	Conc (µgml-1)	Area (mAU.s)	Area (mAU.s)	Area (mAU.s)	Average Area (mAU.s)
1	40	4362.98	4392.53	4519.73	4425.08
2	20	2162.98	2192.53	2219.73	2191.75
3	10	1056.32	1057.87	1177.11	1097,10
4	5	707.04	566.04	569,86	614.31
5	2.5	284.70	286.55	463.72	344.99
6	1.25	177.49	176.21	177.81	177.17
7	0.75	71.89	71.22	71.55	71.55
8	0.375	35.97	35.52	35.52	35.67

STEYX	SLOPE	DL	QL
24.25	118.68	0.67	2.04

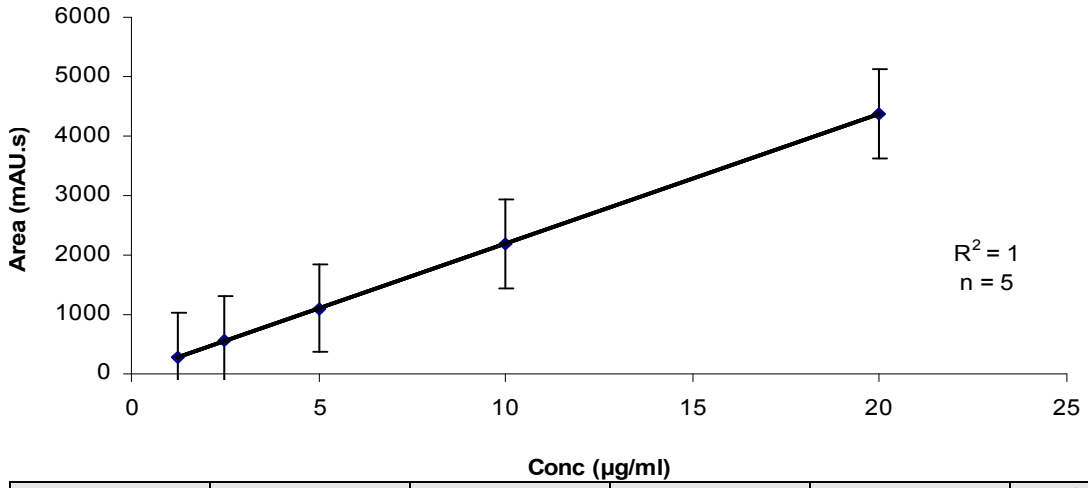
4. Paracetamol in aqueous ethanol (10%).



Sample	Conc (µgml-1)	Area (mAU.s)	Area (mAU.s)	Area (mAU.s)	Average Area (mAU.s)
1	40	2816.73	2845.43	2901.10	2854.42
2	20	1408.36	1408.36	1618.61	1478.45
3	10	694.62	693.53	699.25	695.80
4	5	348.45	347.42	349.56	348.48
5	2.5	177.42	177.55	251.89	202.29
6	1.25	153.21	153.21	153.21	153.21
7	0.75	101.61	91.13	93.76	95.50
8	0.375	22.11	68.88	68.88	53.29

STEYX	SLOPE	DL	QL
41.25	71.66	1.90	5.76

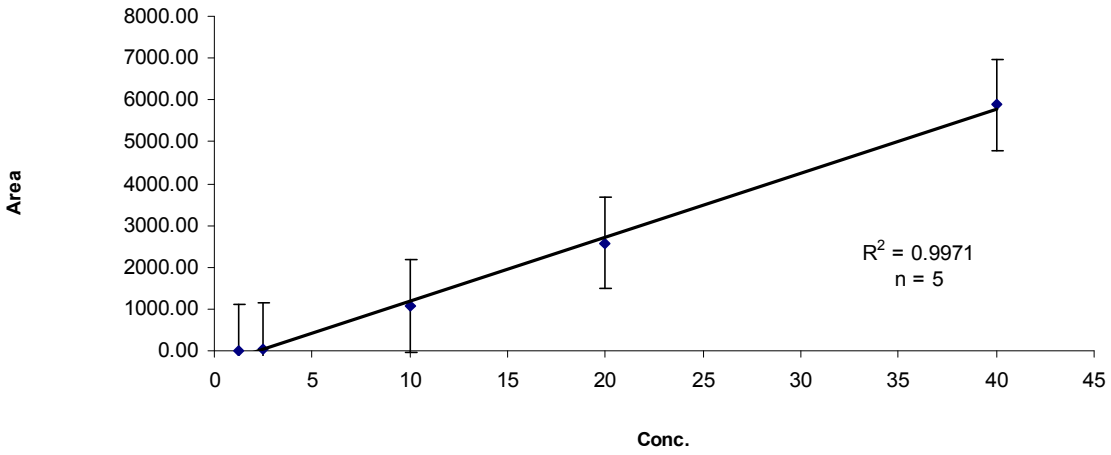
5. Paracetamol in PBS.



Sample	Conc (µgml^{-1})	Area (mAU.s)	Area (mAU.s)	Area (mAU.s)	Average Area (mAU.s)
1	40	8727.70	8710.19	8699.23	8712.37
2	20	4363.85	4365.77	4372.83	4367.48
3	10	2188.90	2190.02	2181.71	2186.88
4	5	1101.90	1100.98	1100.32	1101.07
5	2.50	564.29	563.67	560.76	562.91
6	1.25	288.83	288.99	288.83	288.88
7	0.75	188.64	187.78	185.90	187.44
8	0.38	95.44	94.99	94.33	94.92

STEYX	SLOPE	DL	QL
4.14	217.51	0.06	0.19

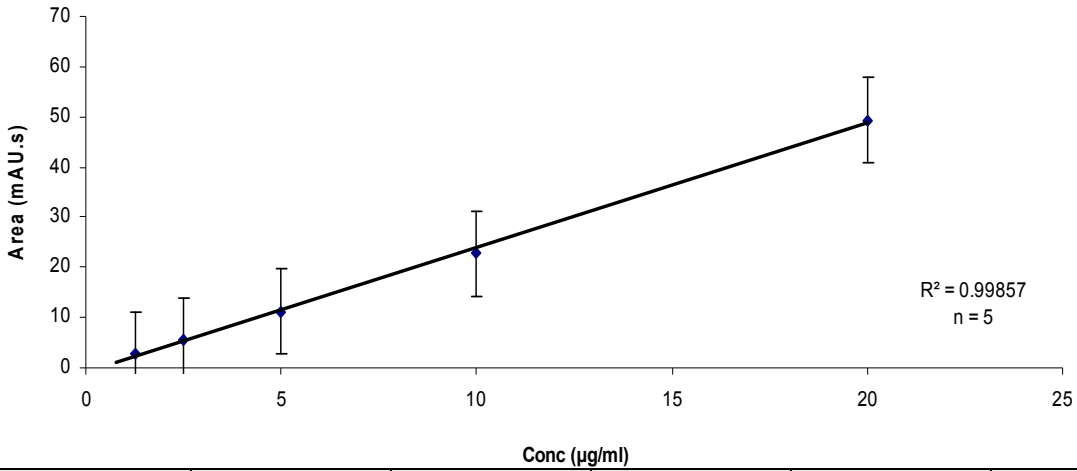
6. Temozolomide in distilled water.



Sample	Conc (µgml^{-1})	Area (mAU.s)	Area (mAU.s)	Area (mAU.s)	Average Area (mAU.s)
1	40	5905.27	5865.32	5872.48	5881.02
2	20	2632.63	2659.74	2439.26	2577.21
3	10	1113.99	1003.07	1113.99	1077.02
4	5	60.72	61.89	63.89	62.17
5	2.5	29.78	31.95	37.63	33.12
6	1.25	14.02	10.46	8.51	11.00
7	0.75	3.36	2.66	2.09	2.71
8	0.375	1.12	1.25	1.32	1.23

STEYX	SLOPE	DL	QL
63.64	145.09	1.45	4.39

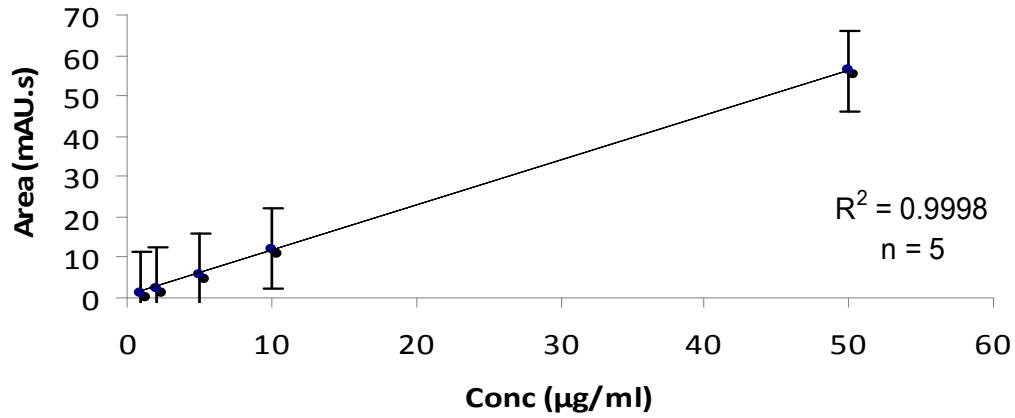
7. Ibuprofen in PBS (pH 7.4).



Sample	Conc (µgml^{-1})	Area (mAU.s)	Area (mAU.s)	Area (mAU.s)	Average Area (mAU.s)
1	40	95.44	93.30	94.21	94.32
2	20	47.41	53.06	47.41	49.29
3	10	22.83	22.83	22.61	22.76
4	5	11.35	11.19	11.24	11.26
5	2.5	5.26	5.66	5.63	5.52
6	1.25	2.75	2.60	2.88	2.74
7	0.75	1.71	1.68	1.70	1.70
8	0.375	1.38	1.33	1.35	1.35

STEYX	SLOPE	DL	QL
0.83	2.48	1.10	3.33

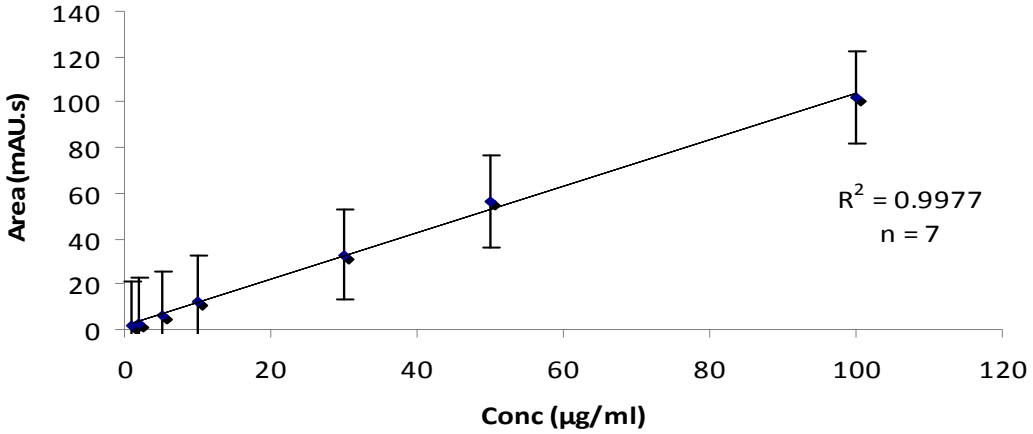
8. Ibuprofen in citric acid (0.1 M) and Na_2HPO_4 (0.2 M) (60 : 40).



Sample	Conc (µgml^{-1})	Area (mAU.s)	Area (mAU.s)	Area (mAU.s)	Average Area (mAU.s)
1	100	101.02	101.50	102.53	101.69
2	50	50.08	51.09	50.88	50.68
3	30	33.53	33.18	34.01	33.57
4	10	12.22	12.27	12.17	12.22
5	5	5.92	5.95	5.90	5.92
6	2	2.46	2.47	2.46	2.46
7	1	1.37	1.36	1.38	1.37
8	0.5	0.69	0.69	0.70	0.69

STEYX	SLOPE	DL	QL
0.40	1.12	1.17	3.55

9. Ibuprofen in citric acid (0.1 M) and Na_2HPO_4 (0.2 M) (89.1 : 10.9).



Sample	Conc (µgml-1)	Area (mAU.s)	Area (mAU.s)	Area (mAU.s)	Average Area (mAU.s)
1	100	102.53	101.50	101.99	102.01
2	50	56.70	55.68	55.98	56.12
3	30	33.10	32.73	33.10	32.98
4	10	12.17	12.27	12.14	12.19
5	5	5.90	5.95	5.89	5.91
6	2	2.46	2.47	2.47	2.46
7	1	1.38	1.36	1.38	1.37
8	0.5	0.67	0.68	0.66	0.67

STEYX	SLOPE	DL	QL
1.97	1.03	6.34	19.21

B. Comparison of HPLC calibration results derived from solubility, stability (ctrl and spent receiver fluid) and permeation experiments.

1. Furosemide in 10% PEG400.

Conc (µgml-1)	Calibration Curve 1 Area (mAU.s)	Calibration Curve 2 Area (mAU.s)	Calibration Curve 3 Area (mAU.s)	Calibration Curve 4 Area (mAU.s)	Calibration Curve 5 Area (mAU.s)	% Precision
50	N/A	9054.40	8793.65	8675.43	9875.23	5.94
40	8000.39	7788.78	7236.98	7698.89	7999.42	4.04
30	N/A	5432.64	5563.75	4476.19	5847.57	11.16
20	3913.38	3976.56	3301.87	3293.56	3965.45	9.73
10	1940.12	1810.88	1350.94	1294.16	2000.56	19.85
5	984.94	869.89	801.99	787.38	99.78	11.21
2	N/A	417.58	364.90	366.78	401.01	6.71
0,5	N/A	89.45	80.67	74.54	91.45	9.37

The area in Calibration Curve1 was calculated at 50 µgml-1. The calculated value was then compared with the actual values measured experimentally each time. The % accuracy was finally determined.

Predicted Area derived from Calibration Curve 1	Areas derived from Calibration Curves 2-5 (Conc =50 µgml-1)	% Accuracy
10889.57	9054.40	20.27
10889.57	8793.65	23.83
10889.57	8675.43	25.52
10889.57	9875.23	10.27

2. Procaine in PBS : water (20:80)

Conc (μgml^{-1})	Calibration Curve 1 Area (mAU.s)	Calibration Curve 2 Area (mAU.s)	Calibration Curve 3 Area (mAU.s)	Calibration Curve 4 Area (mAU.s)	Calibration Curve 5 Area (mAU.s)	% Precision
50	N/A	3912.68	3956.45	4000.46	3956.68	0.91
40	3579.12	2983.37	3145.84	3233.66	2712.67	7.58
30	N/A	2187.56	2222.24	2456.67	2001.78	8.42
20	2031.04	1388.14	1498.50	1588.14	1320.54	8.17
10	934.63	771.71	791.52	798.33	668.53	7.97
5	549.56	341.94	375.34	402.02	349.03	7.46
2	N/A	139.67	140.47	156.77	149.67	5.55
0,5	N/A	42.68	38.80	41.02	35.90	7.41

The area in Calibration Curve1 was calculated at 50 µgml-1. The calculated value was then compared with the actual values measured experimentally each time. The % accuracy was finally determined.

Predicted Area derived from Calibration Curve 1	Areas derived from Calibration Curves 2-5 (Conc =50 µgml-1)	% Accuracy
4974.86	3912.68	27.15
4974.86	3956.45	25.74
4974.86	4000.46	24.36
4974.86	3956.68	25.73

3. Paracetamol in PBS.

Conc (μgml^{-1})	Calibration Curve 1 Area (mAU.s)	Calibration Curve 2 Area (mAU.s)	Calibration Curve 3 Area (mAU.s)	Calibration Curve 4 Area (mAU.s)	Calibration Curve 5 Area (mAU.s)	% Precision
50	N/A	9998.87	9233.33	9112.45	9135.00	4.51
40	8712.37	7943.56	8124.93	8435.39	7134.83	7.02
30	N/A	5991.01	5349.45	4998.99	4589.67	11.34
20	4367.48	3925.43	4001.23	3245.61	3550.50	9.53
10	2186.88	1934.78	1978.79	1824.89	1696.36	6.78
5	1101.07	999.01	901.34	879.89	900.45	5.81
2	N/A	387.55	390.56	320.56	345.78	9.39
0,5	N/A	95.76	93.01	88.99	90.01	3.33

The area in Calibration Curve1 was calculated at 50 µgml-1. The calculated value was then compared with the actual values measured experimentally each time. The % accuracy was finally determined.

Predicted Area derived from Calibration Curve 1	Areas derived from Calibration Curves 2-5 (Conc =50 µgml-1)	% Accuracy
10891.04	9998.87	8.92
10891.04	9233.33	17.95
10891.04	9112.45	19.52
10891.04	9135.00	19.22

4. Ibuprofen in PBS (pH 7.4).

Conc (μgml^{-1})	Calibration Curve 1 Area (mAU.s)	Calibration Curve 2 Area (mAU.s)	Calibration Curve 3 Area (mAU.s)	Calibration Curve 4 Area (mAU.s)	Calibration Curve 5 Area (mAU.s)	% Precision
50	N/A	141.12	142.89	137.01	143.56	2.09
40	94.32	115.32	112.45	110.95	112.87	7.74
30	N/A	71.34	66.78	74.57	68.90	4.76
20	49.29	52.35	55.34	53.68	50.51	4.63
10	22.76	24.32	22.99	24.01	21.03	5.62
5	11.26	11.85	11.65	12.36	12.70	4.78
2	N/A	5.81	5.62	5.41	5.09	5.67
0,5	N/A	1.24	1.27	1.39	1.40	6.18

The area in Calibration Curve1 was calculated at 50 µgml-1. The calculated value was then compared with the actual values measured experimentally each time. The % accuracy was finally determined.

Predicted Area derived from Calibration Curve 1	Areas derived from Calibration Curves 2-5 (Conc =50 µgml-1)	% Accuracy
123.21	141.12	12.70
123.21	142.89	13.77
123.21	137.01	10.07
123.21	143.56	14.18

Appendix 24. *In vitro* permeation study results

1. Procaine HCL

Cell 1							
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²	
0.2		2.36	0.81	0.41	0.16	0.515	
Time (h)	4.00	8.00	24.00	28.00	32.00	36.00	48.00
Peak area	574.30	2633.27	12276.10	22005.30	26496.84	32473.77	51876.63
µg/ml	8.77	68.75	349.62	633.01	763.84	937.94	1503.10
µg/volume sampled	1.75	13.75	69.92	126.60	152.77	187.59	300.62
Total µg	20.71	162.25	825.11	1493.91	1802.67	2213.53	3547.32
Cumulative µg	20.71	164.00	840.62	1579.34	2014.70	2578.33	4099.70
Cumulative µgcm^{-2}	40.21	318.43	1632.14	3066.45	3911.75	5006.10	7960.00

Cell 2							
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²	
0.2		2.36	0.81	0.41	0.16	0.515	
Time (h)	4.00	8.00	24.00	28.00	32.00	36.00	48.00
Peak area	475.99	2898.76	12326.37	18681.57	2249289	30109.11	53443.41
µg/ml	5.91	76.48	351.09	536.20	647.22	869.06	1548.74
µg/volume sampled	1.18	15.30	70.22	107.24	129.44	173.81	309.75
Total µg	13.95	180.50	828.57	1265.43	1527.43	2050.98	3655.02
Cumulative µg	13.95	181.68	845.04	1352.13	1721.37	2374.36	4152.21
Cumulative µgcm^{-2}	27.09	352.75	1640.74	2625.30	3342.21	4610.06	8061.94

Cell 3							
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²	
0.2		2.36	0.81	0.41	0.16	0.515	
Time (h)	4.00	8.00	24.00	28.00	32.00	36.00	48.00
Peak area	1128.75	2888.74	15033.93	22867.26	29740.68	33147.99	55706.58
µg/ml	24.93	76.19	429.95	658.12	858.33	957.58	1614.66
µg/volume sampled	4.99	15.24	85.99	131.62	171.67	191.52	322.93
Total µg	58.82	179.81	1014.69	1553.16	2025.65	2259.88	3810.59
Cumulative µg	58.82	184.79	1034.91	1659.38	2263.49	2669.38	4411.61
Cumulative µgcm^{-2}	114.21	358.79	2009.39	3221.85	4394.80	5182.88	8565.60

Cell 4							
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²	
0.2		2.36	0.81	0.41	0.16	0.515	
Time (h)	4.00	8.00	24.00	28.00	32.00	36.00	48.00
Peak area	522.64	2943.01	11993.18	18185.76	28368.71	31175.15	55585.73
µg/ml	7.27	77.77	341.38	521.76	818.37	900.11	1611.14
µg/volume sampled	1.45	15.55	68.28	104.35	163.67	180.02	322.23
Total µg	17.16	183.54	805.66	1231.35	1931.34	2124.26	3802.29
Cumulative µg	17.16	184.99	822.67	1316.63	2120.98	2477.57	4335.62
Cumulative µgcm^{-2}	33.31	359.18	1597.30	2556.38	4118.10	4810.46	8418.04

Cell 5							
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²	
0.2		2.36	0.81	0.41	0.16	0.515	
Time (h)	4.00	8.00	24.00	28.00	32.00	36.00	48.00
Peak area	507.55	3044.73	12054.64	17680.74	25707.18	27172.46	53766.42
µg/ml	6.83	80.73	343.17	507.05	740.84	783.52	1558.15
µg/volume sampled	1.37	16.15	68.63	101.41	148.17	156.70	311.63

Total µg	16.12	190.53	809.89	1196.63	1748.38	1849.11	3677.22
Cumulative µg	16.12	191.90	827.40	1282.78	1935.94	2184.84	4169.65
Cumulative µgcm^{-2}	31.30	372.59	1606.48	2490.65	3758.83	4242.08	8095.81

Cell 6							
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²	
0.2		2.36	0.81	0.41	0.16	0.515	
Time (h)	4.00	8.00	24.00	28.00	32.00	36.00	48.00
Peak area	ND	2871.64	12390.90	17912.85	21864.78	26491.26	57786.60
µg/ml	0.00	75.69	352.97	513.81	628.92	763.68	1675.24
µg/volume sampled	0.00	15.14	70.59	102.76	125.78	152.74	335.05
Total µg	0.00	178.63	833.00	1212.59	1484.25	1802.28	3953.58
Cumulative µg	0.00	178.63	848.14	1298.32	1672.75	2116.56	4420.59
Cumulative µgcm^{-2}	0.00	346.83	1646.75	2520.82	3247.81	4109.52	8583.03

Average N = 6							
Time	4.00	8.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	41.02	351.43	1688.80	2746.91	3795.58	4660.18	8280.74
SD	38.44	18.30	158.25	314.82	443.52	423.32	274.34
SE	12.16	5.79	50.04	99.55	140.25	133.87	86.76
Cumulative µg	21.13	181.00	869.80	1414.76	1954.87	2400.17	4264.90

2. Paracetamol

Cell 1							
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²	
0.2		2.40	0.83	0.42	0.17	0.541	
Time (h)	6.00	10.00	24.00	26.00	28.00	32.00	48.00
Peak area	1220.30	1317.90	1418.55	1576.82	2042.00	2991.38	4954.43
µg/ml	31.93	35.00	38.18	43.17	57.84	87.79	149.71
µg/volume sampled	6.39	7.00	7.64	8.63	11.57	17.56	29.94
Total µg	76.62	84.01	91.63	103.61	138.83	210.70	359.31
Cumulative µg	76.62	90.39	105.02	124.63	168.48	251.92	418.09
Cumulative µgcm^{-2}	141.69	167.15	194.19	230.47	311.55	465.85	773.12

Cell 2							
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²	
0.2		2.36	0.81	0.41	0.16	0.515	
Time (h)	6.00	10.00	24.00	26.00	28.00	32.00	48.00
Peak area	534.07	705.27	1378.08	1660.74	1837.64	1900.64	3775.28
µg/ml	10.28	15.68	36.90	45.82	51.40	53.39	112.52
µg/volume sampled	2.06	3.14	7.38	9.16	10.28	10.68	22.50
Total µg	24.26	37.00	87.09	108.13	121.30	125.99	265.54
Cumulative µg	24.26	39.06	92.28	120.70	143.04	158.01	308.23
Cumulative µgcm^{-2}	47.10	75.84	179.17	234.36	277.72	306.78	598.47

Cell 3							
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²	
0.2		2.15	0.77	0.39	0.15	0.465	
Time (h)	6.00	10.00	24.00	26.00	28.00	32.00	48.00
Peak area	1057.55	1127.95	1136.67	1145.75	1230.52	1493.53	4232.72
µg/ml	26.79	29.01	29.29	29.57	32.25	40.54	126.95
µg/volume sampled	5.36	5.80	5.86	5.91	6.45	8.11	25.39
Total µg	57.60	62.38	62.97	63.58	69.33	87.17	272.94

Cumulative µg	57.60	67.73	74.13	80.60	92.27	116.55	310.43
Cumulative µgcm^{-2}	123.76	145.53	159.27	173.18	198.24	250.42	666.97

Cell 4							
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²	
0.2		2.25	0.81	0.41	0.16	0.515	
Time (h)	6.00	10.00	24.00	26.00	28.00	32.00	48.00
Peak area	1726.62	1890.23	1945.82	2414.70	2836.84	3012.40	3329.06
µg/ml	47.90	53.06	54.81	69.60	82.92	88.45	98.44
µg/volume sampled	9.58	10.61	10.96	13.92	16.58	17.69	19.69
Total µg	107.77	119.38	123.32	156.60	186.56	199.02	221.50
Cumulative µg	107.77	128.96	143.51	187.75	231.63	260.68	300.84
Cumulative µgcm^{-2}	209.24	250.38	278.65	364.54	449.74	506.13	584.12

Cell 5							
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²	
0.2		2.14	0.77	0.39	0.15	0.465	
Time (h)	6.00	10.00	24.00	26.00	28.00	32.00	48.00
Peak area	772.73	936.03	1388.80	1613.70	2059.76	2492.00	3146.45
µg/ml	17.81	22.96	37.24	44.33	58.40	72.04	92.68
µg/volume sampled	3.56	4.59	7.45	8.87	11.68	14.41	18.54
Total µg	38.11	49.13	79.69	94.88	124.99	154.16	198.34
Cumulative µg	38.11	52.69	87.85	110.48	149.45	190.31	248.90
Cumulative µgcm^{-2}	81.88	113.21	188.75	237.37	321.11	408.90	534.77

Cell 6							
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²	
0.2		2.98	0.83	0.42	0.17	0.541	
Time (h)	6.00	10.00	24.00	26.00	28.00	32.00	48.00
Peak area	956.94	1001.49	1005.44	1059.70	1086.00	1226.08	1870.00
µg/ml	23.62	25.02	25.15	26.86	27.69	32.11	52.42
µg/volume sampled	4.72	5.00	5.03	5.37	5.54	6.42	10.48
Total µg	70.38	74.57	74.94	80.04	82.51	95.68	156.21
Cumulative µg	70.38	79.29	84.67	94.80	102.64	121.35	188.30
Cumulative µgcm^{-2}	130.15	146.63	156.57	175.30	189.80	224.39	348.19

Average N = 6							
Time	6.00	10.00	24.00	26.00	28.00	32.00	48.00
Cumulative µgcm^{-2}	122.30	149.79	192.77	235.87	291.36	360.41	584.27
SD	55.29	58.75	44.75	69.56	95.45	116.77	142.05
SE	17.49	18.58	14.15	22.00	30.18	36.93	44.92
Cumulative µg	62.46	76.36	97.91	119.83	147.92	183.14	295.80

3. Furosemide

* Due to skin depletion, no data were acquired for Cells 3 and 5.

Cell 1						
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²
0.2		2.35	0.82	0.41	0.17	0.528
Time (h)	24.00	26.00	28.00	32.00	36.00	48.00
Peak area	94.56	100.98	326.70	600.00	812.24	1095.39
µg/ml	3.04	3.25	10.53	19.35	26.19	35.33
µg/volume sampled	0.61	0.65	2.11	3.87	5.24	7.07
Total µg	7.14	7.63	24.74	45.46	61.56	83.03

Cumulative µg	7.14	8.23	26.00	48.83	68.79	95.50
Cumulative µgcm^{-2}	13.53	15.60	49.25	92.50	130.32	180.92

Cell 2						
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²
0.2		2.30	0.81	0.41	0.16	0.515
Time (h)	24.00	26.00	28.00	32.00	36.00	48.00
Peak area	14.73	89.54	104.01	323.40	616.84	1035.59
µg/ml	0.46	2.88	3.34	10.42	19.89	33.40
µg/volume sampled	0.09	0.58	0.67	2.08	3.98	6.68
Total µg	1.06	6.62	7.69	23.97	45.75	76.82
Cumulative µg	1.06	6.71	8.36	25.31	49.17	84.22
Cumulative µgcm^{-2}	2.06	13.02	16.22	49.13	95.46	163.52

Cell 3 *						
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²
0.2		2.37	0.80	0.40	0.16	0.502
Time (h)	24.00	26.00	28.00	32.00	36.00	48.00
Peak area	ND	ND	ND	ND	ND	ND
µg/ml	0.00	0.00	0.00	0.00	0.00	0.00
µg/volume sampled	0.00	0.00	0.00	0.00	0.00	0.00
Total µg	0.00	0.00	0.00	0.00	0.00	0.00
Cumulative µg	0.00	0.00	0.00	0.00	0.00	0.00
Cumulative µgcm^{-2}	0.00	0.00	0.00	0.00	0.00	0.00

Cell 4						
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²
0.2		2.31	0.83	0.42	0.17	0.541
Time (h)	24.00	26.00	28.00	32.00	36.00	48.00
Peak area	20.57	90.64	111.81	154.73	588.42	1028.64
µg/ml	0.65	2.91	3.59	4.98	18.97	33.18
µg/volume sampled	0.13	0.58	0.72	1.00	3.79	6.64
Total µg	1.50	6.73	8.30	11.50	43.83	76.64
Cumulative µg	1.50	6.86	9.02	12.93	46.25	82.86
Cumulative µgcm^{-2}	2.78	12.68	16.67	23.92	85.53	153.22

Cell 5 *						
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²
0.2		2.20	0.79	0.40	0.16	0.490
Time (h)	24.00	26.00	28.00	32.00	36.00	48.00
Peak area	ND	ND	ND	ND	ND	ND
µg/ml	0.00	0.00	0.00	0.00	0.00	0.00
µg/volume sampled	0.00	0.00	0.00	0.00	0.00	0.00
Total µg	0.00	0.00	0.00	0.00	0.00	0.00
Cumulative µg	0.00	0.00	0.00	0.00	0.00	0.00
Cumulative µgcm^{-2}	0.00	0.00	0.00	0.00	0.00	0.00

Cell 6						
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²
0.2		2.98	0.83	0.42	0.17	0.541
Time (h)	24.00	26.00	28.00	32.00	36.00	48.00
Peak area	86.41	99.93	320.50	875.59	1120.96	2578.84
µg/ml	2.77	3.21	10.33	28.24	36.16	83.20
µg/volume sampled	0.55	0.64	2.07	5.65	7.23	16.64

Total µg	8.27	9.57	30.78	84.15	107.74	247.92
Cumulative µg	8.27	10.12	31.98	87.41	116.65	264.06
Cumulative µgcm^{-2}	15.29	18.72	59.13	161.64	215.71	488.30

Average n=6						
Time	24.00	26.00	28.00	32.00	36.00	48.00
Cummulative µgcm^{-2}	8.42	15.01	35.32	81.80	131.76	246.49
SD	6.96	2.80	22.16	60.30	59.17	161.61
SE	2.20	0.89	7.01	19.07	18.71	51.11
Cumulative µg	4.49	7.98	18.84	43.62	70.22	131.66

4. Ibuprofen (pH 7.4)

Cell 1								
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²		
0.2		2.00	1.10	0.55	0.30	0.95		
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Peak area	ND	31.073	124.75	227.56	266.95	308.93	371.78	575.18
µg/ml	0.00	29.52	121.98	223.44	262.32	303.75	365.77	566.51
µg/volume sampled	0.00	5.90	24.40	44.69	52.46	60.75	73.15	113.30
Total µg	0.00	59.05	243.95	446.88	524.63	607.50	731.55	1133.03
Cumulative µg	0.00	59.05	249.86	477.18	599.62	734.95	919.75	1394.38
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	0.00	62.17	263.05	502.38	631.28	773.76	968.31	1468.00

Cell 2								
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²		
0.2		2.00	1.10	0.55	0.30	0.950		
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Peak area	59.36	93.46	171.83	310.49	319.04	380.70	471.92	655.34
µg/ml	57.44	91.10	168.44	305.29	313.73	374.58	464.60	645.63
µg/volume sampled	11.49	18.22	33.69	61.06	62.75	74.92	92.92	129.13
Total µg	114.89	182.20	336.88	610.57	627.46	749.16	929.21	1291.26
Cumulative µg	114.89	193.69	366.59	673.97	751.91	936.36	1191.32	1646.30
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	120.95	203.91	385.95	709.55	791.61	985.80	1254.22	1733.22

Cell 3								
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²		
0.2		2.00	1.10	0.55	0.30	0.950		
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Peak area	ND	33.25	134.43	241.52	257.09	264.74	301.21	394.73
µg/ml	0.00	31.67	131.53	237.22	252.59	260.13	296.13	388.43
µg/volume sampled	0.00	6.33	26.31	47.44	50.52	52.03	59.23	77.69
Total µg	0.00	63.34	263.05	474.43	505.17	520.27	592.26	776.86
Cumulative µg	0.00	63.34	269.39	507.07	585.25	650.87	774.88	1018.71
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	0.00	66.69	283.61	533.85	616.15	685.23	815.79	1072.49

Cell 4								
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²		
0.2		2.00	1.10	0.55	0.30	0.950		
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Peak area	ND	71.13	166.74	227.58	291.75	364.38	414.40	474.01

µg/ml	0.00	69.06	163.42	223.46	286.79	358.47	407.84	466.67
µg/volume sampled	0.00	13.81	32.68	44.69	57.36	71.69	81.57	93.33
Total µg	0.00	138.12	326.83	446.91	573.58	716.95	815.67	933.34
Cumulative µg	0.00	138.12	340.65	493.41	664.76	865.49	1035.91	1235.14
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	0.00	145.41	358.63	519.46	699.86	911.19	1090.60	1300.35

Cell 5								
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²		
0.2		2.00	1.10	0.55	0.30	0.950		
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Peak area	8.46	54.80	130.62	303.56	315.62	383.13	401.02	447.71
µg/ml	7.21	52.94	127.77	298.45	310.35	376.98	394.64	440.71
µg/volume sampled	1.44	10.59	25.55	59.69	62.07	75.40	78.93	88.14
Total µg	14.42	105.88	255.54	596.90	620.71	753.97	789.27	881.42
Cumulative µg	14.42	105.88	266.13	633.05	716.54	911.87	1022.57	1193.65
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	15.18	111.47	280.18	666.47	754.37	960.01	1076.56	1256.67

Cell 6								
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²		
0.2		2.00	1.10	0.55	0.30	0.950		
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Peak area	ND	53.23	108.64	225.57	269.29	294.58	316.05	429.01
µg/ml	0.00	106.07	221.47	264.62	289.58	310.78	422.26	422.26
µg/volume sampled	0.00	21.21	44.29	52.92	57.92	62.16	84.45	84.45
Total µg	0.00	212.15	442.95	529.24	579.17	621.55	844.51	844.51
Cumulative µg	0.00	212.15	464.16	594.75	697.60	797.91	844.51	1167.47
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	0.00	223.35	488.67	626.16	734.43	840.03	889.10	1229.11

Average N = 6								
Time	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	22.69	135.50	343.35	592.98	704.62	859.34	1015.76	1343.31
SD	48.52	68.10	86.22	86.26	69.51	115.61	157.76	229.48
SE	15.34	21.53	27.27	27.28	21.98	36.56	49.89	72.57
Cumulative µg	21.55	128.70	326.13	563.24	669.28	816.24	964.82	1275.94

5. Ibuprofen (pH 4.2)

Cell 1								
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²		
0.2		2.00	1.10	0.55	0.30	0.950		
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Peak area	8.46	34.91	41.66	57.20	77.40	89.44	91.98	132.44
µg/ml	7.21	33.31	39.97	55.31	75.24	87.13	89.64	129.57
µg/volume sampled	1.44	6.66	7.99	11.06	15.05	17.43	17.93	25.91
Total µg	14.42	66.62	79.95	110.62	150.48	174.26	179.28	259.14
Cumulative µg	14.42	66.62	86.61	125.28	176.20	215.03	237.47	335.26
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	15.18	70.14	91.18	131.89	185.51	226.38	250.01	352.96

Cell 2								
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²		
0.2		2.00	1.10	0.55	0.30	0.950		
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Peak area	ND	25.46	37.57	56.90	61.58	81.90	98.65	132.61
µg/ml	0.00	23.98	35.94	55.01	59.63	79.69	96.22	129.73
µg/volume sampled	0.00	4.80	7.19	11.00	11.93	15.94	19.24	25.95
Total µg	0.00	47.96	71.88	110.02	119.27	159.37	192.44	259.47
Cumulative µg	0.00	47.96	76.67	122.00	142.25	194.29	243.29	329.56
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	0.00	50.50	80.72	128.45	149.76	204.54	256.13	346.96

Cell 3								
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²		
0.2		2.00	1.10	0.55	0.30	0.950		
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Peak area	ND	15.23	31.99	67.75	81.02	86.90	96.90	117.82
µg/ml	0.00	13.89	30.43	65.72	78.82	84.62	94.49	115.14
µg/volume sampled	0.00	2.78	6.09	13.14	15.76	16.92	18.90	23.03
Total µg	0.00	27.78	60.85	131.44	157.64	169.24	188.97	230.27
Cumulative µg	0.00	27.78	63.63	140.31	179.65	207.01	243.67	303.87
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	0.00	29.25	66.99	147.71	189.14	217.94	256.53	319.91

Cell 4								
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²		
0.2		2.00	1.10	0.55	0.30	0.950		
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Peak area	ND	22.45	47.04	56.10	84.51	89.33	130.62	154.84
µg/ml	0.00	21.01	45.28	82.27	87.01	127.77	151.67	151.67
µg/volume sampled	0.00	4.20	9.06	16.45	17.40	25.55	30.33	30.33
Total µg	0.00	42.03	90.56	164.53	174.03	255.54	303.34	303.34
Cumulative µg	0.00	42.03	94.76	177.79	203.74	302.65	376.01	333.68
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	0.00	44.25	99.77	187.18	214.50	318.63	395.87	351.30

Cell 5								
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²		
0.2		2.00	1.10	0.55	0.30	0.950		
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Peak area	5.31	12.46	40.75	66.51	74.70	79.65	104.41	152.48
µg/ml	4.09	11.16	39.08	64.50	72.58	77.47	101.90	149.34
µg/volume sampled	0.82	2.23	7.82	12.90	14.52	15.49	20.38	29.87
Total µg	8.19	22.32	78.15	129.00	145.16	154.93	203.79	298.68
Cumulative µg	8.19	22.32	80.39	139.04	168.11	192.39	256.75	372.02
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	8.62	23.49	84.63	146.38	176.98	202.55	270.31	391.66

Cell 6								
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²		
0.2		2.00	1.10	0.55	0.30	0.950		
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Peak area	ND	23.76	44.30	66.51	84.64	84.12	118.77	165.20
µg/ml	0.00	22.31	42.58	64.50	82.39	82.39	116.08	161.90

µg/volume sampled	0.00	4.46	8.52	12.90	16.48	16.48	23.22	32.38
Total µg	0.00	44.61	85.16	129.00	164.77	164.77	232.15	323.79
Cumulative µg	0.00	44.61	89.62	141.97	186.19	207.13	290.99	405.84
Time (h)	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	0.00	46.97	94.35	149.47	196.02	218.06	306.35	427.27

Average N = 6								
Time	4.00	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	3.97	44.10	66.00	148.51	185.32	231.35	289.20	365.01
SD	6.48	16.57	11.63	20.88	21.51	43.70	56.08	38.15
SE	2.05	5.24	3.68	6.60	6.80	13.82	17.73	12.07
Cumulative µg	3.77	41.89	81.95	141.07	176.02	219.75	274.70	346.70

6. Ibuprofen (pH 2.6)

Cell 1							
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²	
0.2		2.00	1.10	0.55	0.30	0.950	
Time (h)	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Peak area	ND	18.83	29.61	40.10	50.20	67.88	110.62
µg/ml	0.00	17.24	27.92	38.30	48.31	65.81	108.14
µg/volume sampled	0.00	3.45	5.58	7.66	9.66	13.16	21.63
Total µg	0.00	34.48	55.84	76.61	96.62	131.63	216.28
Cumulative µg	0.00	34.48	59.29	85.64	113.31	157.98	255.80
Time (h)	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	0.00	36.30	62.42	90.16	119.30	166.33	269.30

Cell 2							
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²	
0.2		2.00	1.10	0.55	0.30	0.950	
Time (h)	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Peak area	4.32	26.82	36.54	44.58	53.89	70.54	125.80
µg/ml	2.87	25.16	34.78	42.74	51.95	68.45	123.17
µg/volume sampled	0.57	5.03	6.96	8.55	10.39	13.69	24.63
Total µg	5.75	50.31	69.56	85.48	103.91	136.90	246.33
Cumulative µg	5.75	50.89	75.16	98.04	125.02	168.40	291.52
Time (h)	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	6.05	53.57	79.13	103.21	131.62	177.29	306.92

Cell 3							
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²	
0.2		2.00	1.10	0.55	0.30	0.950	
Time (h)	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Peak area	ND	22.08	30.41	44.57	52.80	71.43	114.56
µg/ml	0.00	20.46	28.71	42.74	50.88	69.33	112.03
µg/volume sampled	0.00	4.09	5.74	8.55	10.18	13.87	22.41
Total µg	0.00	40.92	57.42	85.47	101.76	138.66	224.07
Cumulative µg	0.00	40.92	61.51	95.30	120.14	167.21	266.49
Time (h)	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	0.00	43.08	64.76	100.34	126.48	176.04	280.56

Cell 4							
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²	
0.2		2.00	1.10	0.55	0.30	0.950	
Time (h)	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Peak area	ND	24.86	35.05	46.70	55.25	71.58	117.60
µg/ml	0.00	23.21	33.31	44.84	53.31	69.48	115.05
µg/volume sampled	0.00	4.64	6.66	8.97	10.66	13.90	23.01
Total µg	0.00	46.42	66.62	89.69	106.61	138.96	230.10
Cumulative µg	0.00	46.42	71.26	100.99	126.89	169.89	274.93
Time (h)	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	0.00	48.87	75.02	106.32	133.59	178.86	289.45

Cell 5							
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²	
0.2		2.00	1.10	0.55	0.30	0.950	
Time (h)	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Peak area	2.04	23.34	32.90	43.16	51.38	69.59	105.68
µg/ml	0.61	21.71	31.17	41.33	49.47	67.51	103.24
µg/volume sampled	0.12	4.34	6.23	8.27	9.89	13.50	20.65
Total µg	1.23	43.42	62.35	82.66	98.94	135.01	206.49
Cumulative µg	1.23	43.54	66.81	93.36	117.91	163.87	248.85
Time (h)	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	1.29	45.84	70.34	98.29	124.14	172.53	261.99

Cell 6							
Volume sampled/ml	Franz Cell	Volume (ml)	Diameter	Radius	(Radius)²	Area cm²	
0.2		2.00	1.10	0.55	0.30	0.950	
Time (h)	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Peak area	ND	15.96	28.13	41.36	50.20	66.81	104.60
µg/ml	0.00	14.40	26.45	39.55	48.31	64.75	102.17
µg/volume sampled	0.00	2.88	5.29	7.91	9.66	12.95	20.43
Total µg	0.00	28.79	52.90	79.10	96.62	129.51	204.35
Cumulative µg	0.00	28.79	55.78	87.27	112.70	155.25	243.04
Time (h)	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	0.00	30.31	58.72	91.87	118.65	163.44	255.87

Average N = 6							
Time	8.00	12.00	24.00	28.00	32.00	36.00	48.00
Cumulative µgcm^{-2}	1.22	43.00	68.40	98.37	125.63	172.42	277.35
SD	2.42	8.49	7.82	6.33	6.18	6.26	18.94
SE	0.77	2.68	2.47	2.00	1.95	1.98	5.99
Cumulative µg	1.16	40.84	64.97	93.43	119.33	163.77	263.44